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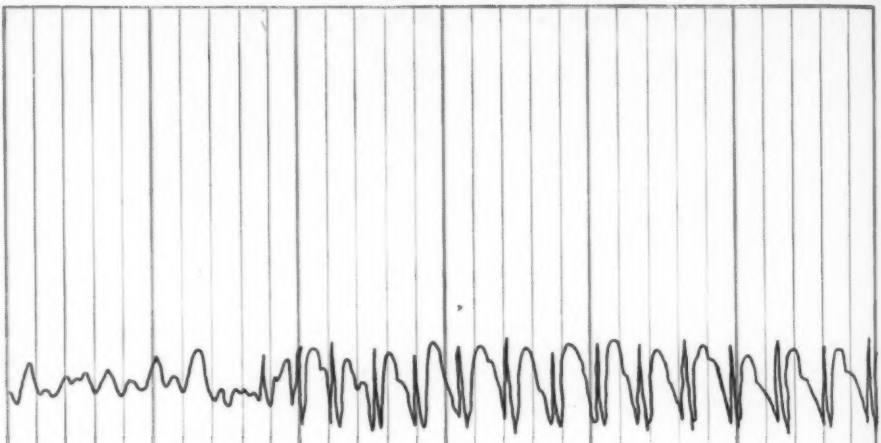

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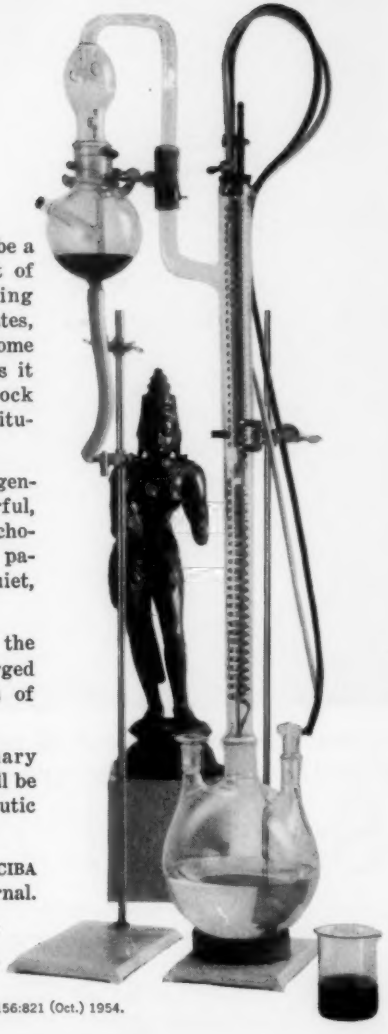

1. Noce, R. H., Williams, D. B., and Rapaport, W.: J. A. M. A.: 156:821 (Oct.) 1954.

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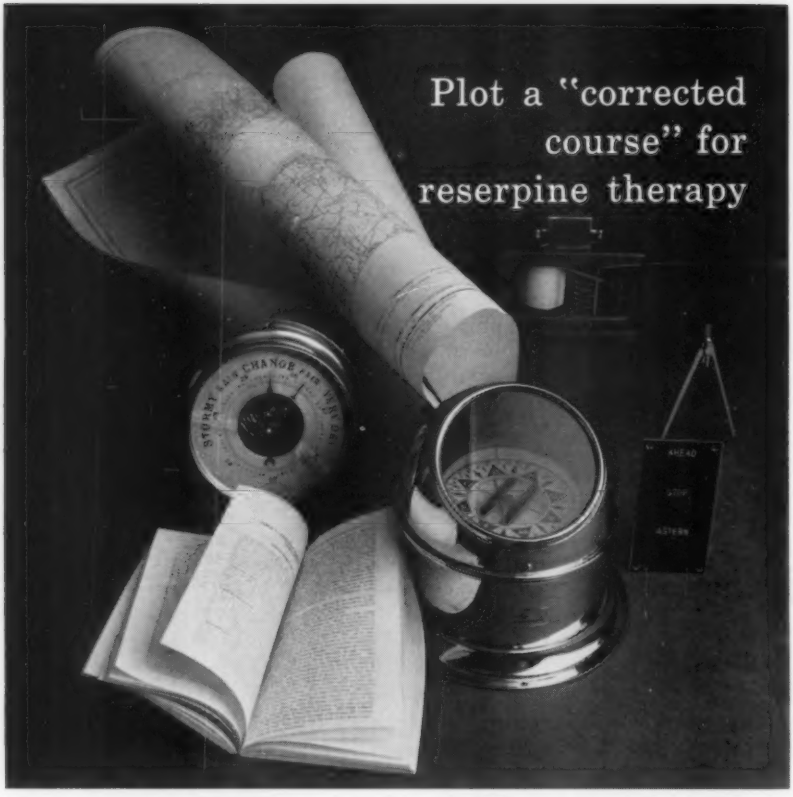

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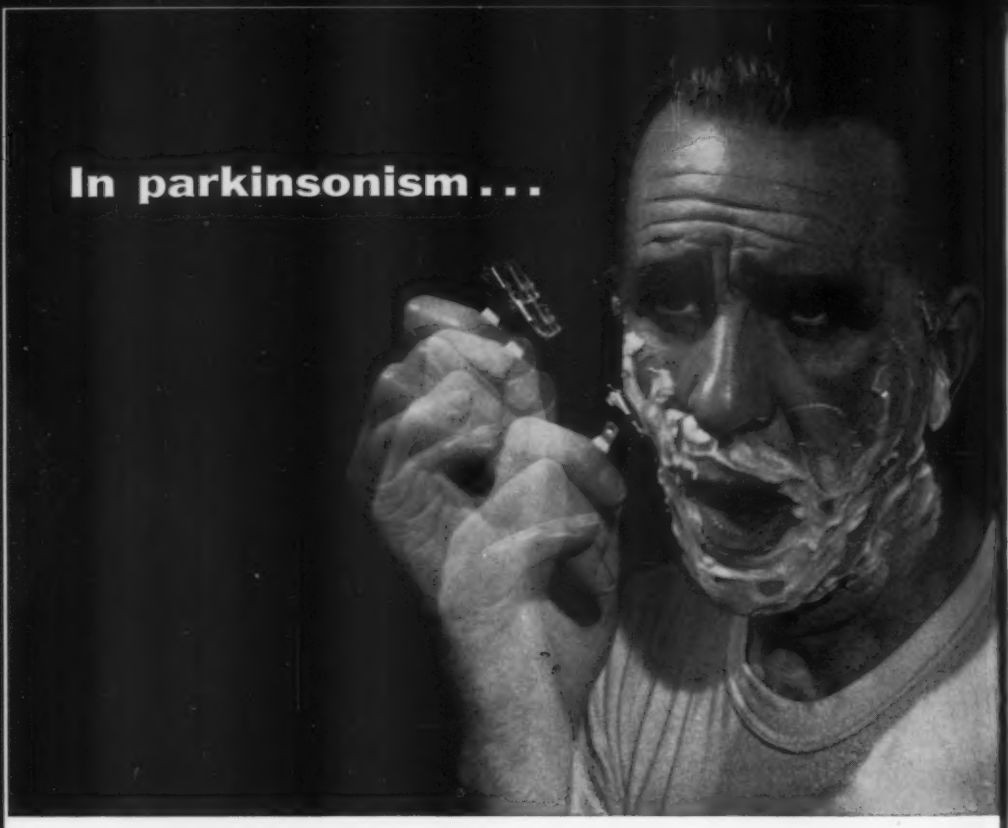

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1. Gallager, D. J. A., and Palmer, H.: New Zealand M. J. 49:531 (Oct.) 1950. 2. Sigwald, J.: Presse méd. 59:819 (Sept. 17) 1949. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. 247:98 (July 17) 1952.

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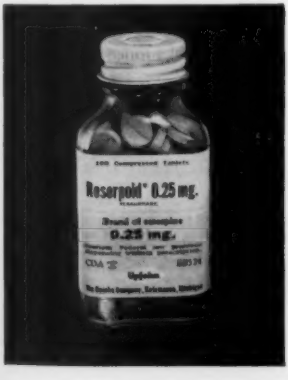

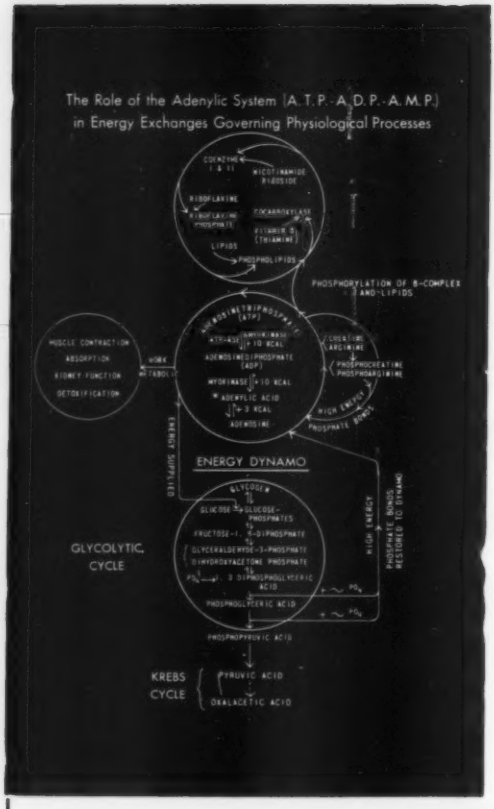

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Volume 5 Neurology *Number 3*

Effects of Photic Stimulation During Sleep

A Study of Normal Subjects and Epileptic Patients

Ernst A. Rodin, M.D., David D. Daly, M.D. and Reginald G. Bickford, M.B.

In 1934 Adrian and Matthews[1] observed that if a rhythmically flashing light was shined in the eyes of a subject, waves having the same frequency as the flashing light appeared in the electroencephalogram. This phenomenon has been called "photic driving." It appears maximally in the occipital and parietal regions and usually as a bilaterally symmetrical rhythm. However, the term "photic driving" is not entirely satisfactory, since to some authors it has implied a response intimately linked with alpha rhythm mechanisms. As this hypothesis has not been substantiated as yet, in this study we have used the term "photic response" which does not necessarily imply any connection with alpha rhythms.

The observations of Adrian and Matthews have been extended by a number of authors.[2-4] In general, when brief pulses of light are flashed in the eye at relatively slow rates (less than one flash per second), complex polyphasic responses can be recorded from electrodes placed in the occipital regions of the skull. As the flash rate is increased, the responses tend to fuse and assume more sinusoidal forms. The shapes of the sinusoidal forms may be distorted by the presence of harmonic or subharmonic frequencies of the flash rate. Photic responses may be seen over a wide range of frequencies, and they frequently persist after closure of the eyes, although under those circumstances recognition may be difficult because of mixture with spontaneous alpha rhythms.

Another important effect of photic stimulation is the initiation of convulsive manifestations in certain individuals. These may take the form of myoclonic jerkings, petit mal attacks, or generalized convulsions.[5-9] In some patients the degree of sensitivity to light is such that

From the sections of neurology and physiology, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

symptoms are manifest under the conditions of everyday life. The flickering light resulting from driving through an avenue of trees when the sun is shining or looking at sunlight reflected on water or snow may be sufficient to produce an epileptic seizure. This condition has been termed "photo-epilepsy."

Although considerable study has been devoted to the effect of light stimulation on normal persons and epileptic patients during the waking state, relatively little attention has been paid to the effect of photic stimulation in sleep. The photic response during sleep of normal subjects was investigated by Daly in 1951[2] and by Brazier in 1953.[10] So far as could be determined, the literature does not contain any reports about the effects of light stimulation in epileptic patients during sleep. An investigation of this topic appeared interesting for two main reasons. The first was to determine whether conduction in the optic pathways to the cortex was unimpaired during sleep or whether the cortex is in fact functionally "deafferentated" as has been suggested by Bremer.[11] The second reason was connected with the fact that spontaneous epileptic discharges are often increased during the period of drowsiness and sleep. This naturally raises the question as to whether the electroencephalographic activating effect of sleep could be enhanced by photic stimulation during this period. Furthermore, it was hoped that some insight might be gained into the mechanisms involved in photo-epilepsy in particular and the state of sleep in general.

MATERIAL AND METHOD OF STUDY

Five normal persons and 76 epileptic patients were examined. The epileptic patients were of two types: 30 patients who showed various degrees of sensitivity to light during the waking recording, and 46 who gave no evidence of sensitivity to light either clinically or under laboratory conditions. If spontaneous sleep did not occur, epileptic patients were given secobarbital sodium (Seconal) sodium) by mouth in doses ranging between 50 and 200 mg. Two patients received amobarbital sodium (Amytal sodium) by mouth in doses of 125 and 200 mg., respectively.

Recordings were made with an eight-channel Grass electroencephalograph. Fourteen electrodes were used, consisting of five pairs of electrodes equally spaced and placed in lines 4 cm. from the midline, one pair of electrodes in the temporal regions, and one pair of electrodes on the ears. Both scalp-to-scalp and scalp-to-ear linkages were used. Photic stimulation was performed with the stimulator described by Bickford and Moffet.[12] The flashes were of brief duration (50 microseconds) and the rate of stimulation could be varied from one to 30 flashes per second. The intensity of the flash was approximately 250,000 foot candles.

The normal persons and epileptic patients were tested both with the eyes open and the eyes closed in the waking state. During sleep special care was taken to keep a constant distance of 15 cm. between the light and the eyes in spite of shifts in the sleepers' positions. All tests were made in a dimmed room. In some instances a further reduction of illumination was made to promote sleep.

The normal subjects went to sleep spontaneously. In the studies made on normal persons either an Ediswan automatic low frequency wave analyzer or, for one subject, an Offner type of analyzer was employed to quantitate the

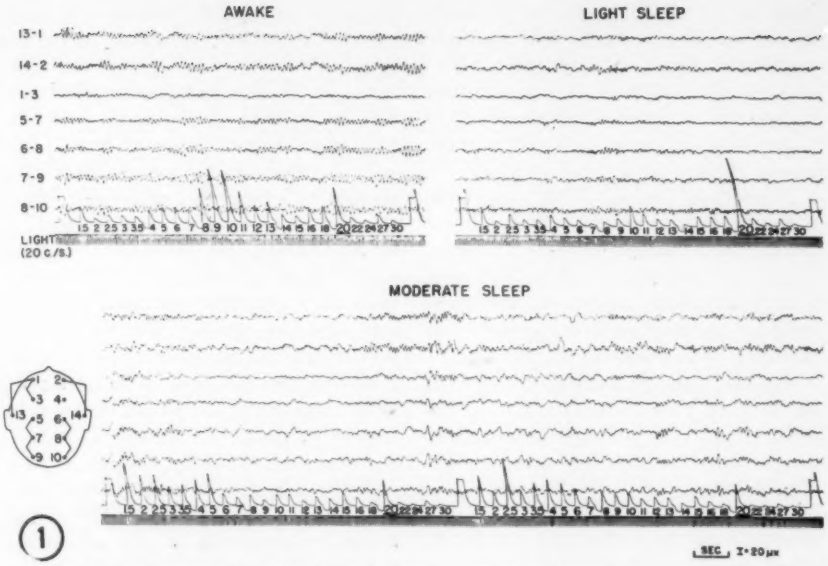

FIG. 1. Photic responses in various phases of sleep demonstrated by automatic frequency analysis. Channel 7 is analyzed.

photic responses in the presence of rhythms appearing during sleep, since visual analysis was unreliable.

RESULTS

Normal subjects. All persons tested showed photic responses during sleep. In some instances the response could be seen clearly by direct observation of the primary tracings. It occurred over a wide range of frequencies from 2 to 20 cycles per second. The amplitude of the responses as indicated by the analyzer deflections decreased as the subject passed from the light to the deep stages of sleep, although the series of studies is not large enough to permit reliable generalization. Figure 1 illustrates this point. In this subject recordings were made during transition from the waking state to sleep while the light was continuously flashing at the rate of 20 flashes per second. The rate of 20 flashes per second was chosen because it was outside the spectrum of frequencies occurring spontaneously in this subject either in the waking state or during sleep. The appearance of a deflection of the analyzer pen at the 20-cycle frequency related to light stimulation was taken to indicate the occurrence of a specific light response. With the disappearance of the alpha frequencies and the onset of light sleep, the photic response becomes more prominent. In the spindle stage of sleep it is somewhat diminished but can still be observed clearly.

Since the alpha rhythm seems in some way related to the conscious state, it was interesting to observe whether there would be any photic responses to these frequencies during sleep and whether

these responses, if they occurred, would arouse the subject. While well developed responses to flash rates in the subject's alpha range could be seen in some instances, there was no evidence that their occurrence was associated with any apparent change in the level of sleep.

From these limited observations we conclude that photic responses can occur during sleep, although they may be reduced in amplitude when compared with the waking state. The responses tend to decrease with deepening sleep but may be detected in deep stages.

Epilepic patients sensitive to light. In all 30 cases photic stimulation was carried out not only during sleep but also immediately before the patient was allowed to go to sleep, and in most cases immediately after awakening in order to detect any long-term changes in the threshold of sensitivity to light. During sleep the flash frequencies used for most epileptic patients were limited to those which had been most effective in eliciting pathologic responses in the waking state.

Findings: Patients awake. The patients whose salient features are summarized in table 1 presented two main types of sensitivity to light in the waking state. The majority had a photoconvulsive type of response, as indicated by the occurrence of generalized, high-voltage, complex, paroxysmal discharges elicited by stimulation with light, which usually conformed to the atypical or classical discharges of spike and wave pattern. Four patients showed the photomyoclonic response described by Bickford and associates.[13] This consists of high voltage spike discharges recorded from the anterior regions of the head which apparently arise from the muscles around the eyes. As shown in table 1, the electroencephalographic findings for resting patients in the waking state ranged from normal through diffuse nonspecific dysrhythmia to spike and wave patterns. Six of these patients had clinical photo-epilepsy. Four of them induced their seizures themselves by rhythmically waving their hands before their eyes while looking at the sun. The other two had attacks while driving through avenues of trees while the sun

TABLE 1
RESULTS OF PHOTIC STIMULATION DURING SLEEP IN 30 EPILEPTIC PATIENTS SENSITIVE TO LIGHT*

Case	Age, sex	Type of seizure	Resting EEG	Photic stimulation							Light sensitivity returns
				Patient awake				Patient asleep			
				EEG response	Relation of E. O. : E. C.	Receiving anticonvulsive drug	Seizures induced	Medication to induce sleep	EEG response	Seizures induced	
1	18F	G.M.;P.M.	N.	PC.	E.O.=E.C.	0	0	Seconal 100 mg.	0	0	+
2	10F	P.M. sick triplet	D.	PC.	E.O.=E.C.	0	0	None	0	0	Not tested
3	10F	Normal triplet	D.	PC.	E.O.=E.C.	0	0	Seconal 50 mg.	0	0	0
4	6F	P.M.	S.W.	PC.	E.O.=E.C.	0	0	Seconal 50 mg.	±	0	+
5	5F	G.M.	S.W.	PC.	E.O.>E.C.	0	Jerking	Seconal 100 mg.	0	0	±
6	16F	G.M.;P.M.	S.W.	PC.	E.O.>E.C.	0	0	Seconal 100 mg.	0	0	±
7	23F	G.M.	S.W.	PC.	E.O.=E.C.	+	Jerking	Seconal 100 mg.	±	0	Not tested

TABLE 1—(*Continued*)

Case	Age, sex	Type of seizure	Resting EEG	Photic stimulation							Light sensitivity returns
				Patient awake				Patient asleep			
				EEG response	Relation of E. O. : E. C.	Receiving anticonvulsive drug	Seizures induced	Medication to induce sleep	EEG response	Seizures induced	
8	8F	G.M.;P.M.; hand waver	S.W.	PC.	E.O.>E.C.	0	Jerking	None	+	±	+
9	57F	G.M.	S.W.	PC.	E.O.<E.C.	0	Jerking	Seconal 100 mg.	±	0	+
10	4F	G.M.	S.W.	PC.	E.O.=E.C.	+	0	None	±	0	±
11	17M	G.M.;P.M.	S.W.	PC.	E.O.=E.C.	+	Jerking	Seconal 100 mg.	0	0	±
12	9M	P.M.	S.W.	PC.	E.O.=E.C.	0	P.M.	None	+	0	+
13	20F	G.M.;P.M.	S.W.	Pmyoc.	Once only with E.O.	+	Myoclonus of eyelids	None	0	0	+†
14	6M	G.M. (mentally retarded)	S.W.	PC.	E.O.=E.C.	+	Jerking	None	±	±	+
15	14F	G.M.;P.M.	S.W.	PC.	E.O.=E.C.	0	Jerking	Seconal 100 mg.	±	0	+
16	12F	G.M.;P.M.	S.W.	PC.	E.O.=E.C.	+	P.M.	None	±	0	+
17	16M	P.M.;G.M.; hand waver	S.W.	PC.	E.O.=E.C.	0	Jerking	Amytal 125 mg.	±	±	Not tested
18	20F	G.M.	S.W.	PC.	E.O.=E.C.	+	P.M.	Amytal 200 mg.	±	0	Not tested
19	14M	Unverricht's myoclonic epilepsy	Bilat. frontal spikes; D.	Pmyoc.	E.O.=E.C.	0	Jerking	None	+	±	+
20	11M	P.M.; hand waver	S.W.	PC.	E.O.=E.C.	0	Jerking	None	+	0	+
21	8F	G.M. (mental deterioration)	S.W.	Pmyoc.	E.O.=E.C.	+	Jerking	None	+	0	Not tested
22	6M	P.M.; hand waver	S.W.	PC.	E.O.=E.C.	+	P.M.	None	±	0	+
23	13F	G.M. (mentally retarded)	S.W.	PC.	E.O.=E.C.	+	Jerking	Seconal 100 mg.	0	0	+
24	26F	G.M.	S.W.	Pmyoc.	E.O.<E.C.	0	Jerking	Seconal 100 mg.	0	0	+
25	7F	P.M.	S.W.	PC.	E.O.=E.C.	0	P.M.	Seconal 200 mg.	0	0	Not tested
26	27M	G.M.	Sharp waves bi-occipital	Sharp waves bi-occipital	E.O.=E.C.	0	0	Seconal 200 mg.	+	0	+
27	22M	G.M.	Sharp waves bi-occipital	Sharp waves bi-occipital	E.O.=E.C.	0	Aura	None	+	0	+
28	10F	P.M.	S.W.	PC.	E.O.=E.C.	0	P.M.	None	0	0	±
29	19F	G.M.	S.W.	PC.	E.O.=E.C.	0	G.M.	Seconal 100 mg.	0	0	±
30	38F	G.M.	D.	PC.	E.O.=E.C.	+	0	None	0	0	0

*Legend: G.M., grand mal; P.M., petit mal; N., normal; D., dysrhythmia; S.W., spike wave; PC., photoconvulsive response; Pmyoc., photomyoclonic response; E.O., eyes open; E.C., eyes closed; +, present; 0, absent or none; ±, reduced.

†Photoconvulsive response with petit mal seizures right after awakening.

was shining. Twenty-two patients had attacks under laboratory conditions. These consisted mainly of generalized myoclonic jerkings of the body and extremities, petit mal seizures, and one grand mal seizure.

The electroencephalograms of two patients showed sharp wave foci in the occipital regions in the resting record. In both patients when the light was flashed at rates slower than six flashes per second, a sharp wave in the occipital regions followed each flash, indicating the occurrence of a triggering effect.

Findings: Patients asleep. During sleep 17 patients showed electroencephalographic evidence of sensitivity to light and 13 did not. These differences in response are illustrated in figures 2 and 3. When sensitivity to light persisted, it was in many instances definitely reduced compared with the degree of sensitivity in the waking state. It usually took a longer period of stimulation to produce an effect comparable to that seen in the waking state. In addition the discharges tended to be of shorter duration. Three patients (cases 16, 28, and 29) were observed throughout the entire period of going to sleep; the light was flashed at 15 flashes per second for two to three seconds every 20 seconds. When these patients settled down to rest and entered the stage of drowsiness, the light stimulation became ineffective in producing discharges. The periods of stimulation were then extended to five to six seconds, at the end of which period the pathologic paroxysms recurred. Later this stimulation was effective only intermittently. When a medium deep stage of sleep was reached, no paroxysms could be elicited in two cases, while they persisted intermittently in one case. The spontaneous epileptic discharges did not follow the same pattern in relation to deepening sleep, since the frequency of appearance was increased during drowsiness and early sleep.

The two patients whose focal occipital sharp waves could be triggered by light stimulation during the waking state showed the same effect during sleep. In one of these patients there was a tendency for the triggering to be more effective during sleep.

One of these 30 patients (case 13) was unique inasmuch as she showed only minimal photomyoclonic responses during the waking state and none during sleep. Immediately after awakening, however, the patient had a marked photoconvulsive response which was associated with a petit mal seizure. This responsive condition persisted for two minutes after awakening, then disappeared abruptly and could no longer be elicited. The study was repeated with identical results. This patient had observed that most of her seizures occurred

TABLE 2
RELATION OF PREMEDICATION AND DEGREE OF LIGHT SENSITIVITY TO CHANGES IN SLEEP

	Medicated sleep			*Spontaneous sleep*		
	Present	*Reduced*	*Absent*	*Present*	*Reduced*	*Absent*
Mildly sensitive	0	0	1	0	1	3
Moderately sensitive	1	1	2	1	0	0
Severely sensitive	0	5	6	5	3	1
Total	7		9	10		4

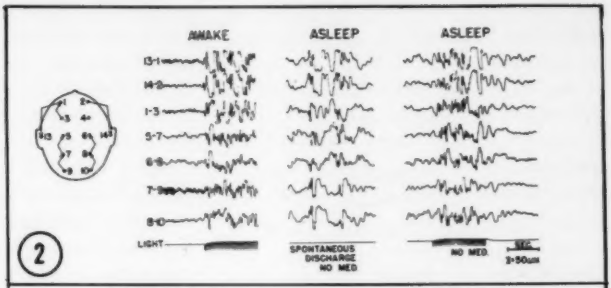

FIG. 2. *Case 20.* Photoconvulsive response retained during sleep.

FIG. 3. *Case 28.* Photoconvulsive response abolished during sleep.

after awakening but while she was still in bed.

One patient (case 3) is included in the group of epileptic patients because of sensitivity to light although she had not experienced any seizures up to the time when she was last examined. She was, however, one of triplet sisters of whom one sister (case 2) had petit mal and was sensitive to light. The third sister was a normal girl without any history of seizures and without sensitivity to light.

Since 43 per cent of patients became insensitive to light stimulation during sleep, the question arose whether pre-sleep sedation or anticonvulsant medication could be a contributing factor. A survey of the 30 patients indicated no significant difference in regard to changes with sleep between the group who received anticonvulsant medication

and those not medicated. However, the medication required to produce sleep did appear to have a significant influence on the findings as indicated by table 2. A tendency for preservation of sensitivity to light when sleep was obtained spontaneously can be noted, whereas when premedication was used sensitivity to light was absent in a relatively greater number of patients.

Medication apparently had some suppressive effect on the light-induced discharges during sleep. The degree of light sensitivity was evaluated by placing the patients into three subgroups, namely, those who were mildly light sensitive, those moderately light sensitive, and those severely light sensitive. "Mildly light sensitive" refers to patients who in the waking state had only occasional pathologic responses to light in the electroencephalogram without clinical accompaniments. "Moderately light sensitive" refers to patients who showed pathologic electroencephalographic responses without clinical accompaniments in at least 70 per cent of all the stimulation periods. "Severely light sensitive" indicates that the electroencephalograms showed pathologic responses associated with clinical seizures in at least 90 per cent of all the stimulation periods. The correlation between the degree of light sensitivity and its presence in spontaneous or medicated sleep can be seen in table 2. The severity of the pathologic process, as well as premedication, had an influence on the pathologic responses during sleep. If light sensitivity was mild in the waking state, it tended to disappear even in spontaneous sleep. If it was severe, it tended to be present to the same degree or reduced in spontaneous sleep; while in medicated sleep, it was either reduced or absent. Apparently the threshold to photically induced seizures is elevated in spontaneous sleep and still more so if the patient has received medication. It may be that the patient who received premedication reached a deeper level of sleep and that the differences in the photic responses could be attributable to this factor; however, there was no electroencephalographic evidence to support this contention. Tracings from patients who slept spontaneously and from those who had received premedication were indistinguishable.

Seizure discharges that were associated with clinical manifestations in the waking state became less effective in producing outward signs during sleep. Patients who had petit mal with fluttering of the eyelids while awake showed no clinical signs when asleep. Of 13 patients with generalized myoclonic jerking in the waking state, four showed a reduction in duration and intensity of it during sleep while in nine patients there were no muscular signs. Again there was a difference between medicated and spontaneous sleep. Eight of these 13 patients had received medication; jerking was absent in seven and reduced in one. Jerking was absent in two and reduced in three of the five patients who slept spontaneously.

Epileptic patients not sensitive to light. Sensitivity to light is unchanged, reduced, or absent during sleep. Although sensitivity to light did not increase in any case during sleep, it was important to verify this in a larger group of epileptic patients who had no evidence of sensitivity to light in the waking recordings. The 46 epileptic patients who constitute this second group had various types of convulsive disorders. These patients were tested in the same

manner as the patients sensitive to light. Thirty-three went to sleep spontaneously while 13 patients needed sedation. None of these patients showed abnormal responses to light during or after sleep.

COMMENT

Demonstration of photic responses in the occipital regions of normal persons during sleep is of interest for its bearing on the controversy concerning the degree of cortical deafferentation in the sleep process. In 1936 Bremer[11] claimed that sleep resulted from progressive reduction of the afferent inflow to the cortex. This view has been challenged by the work of Magoun[14] who has shown that sleep can be induced in animals by lesions of the reticular system in the presence of intact lateral columns and that, contrariwise, deafferentation of the cortex by section of the lateral columns does not in itself induce the sleeping state. Our findings on normal subjects suggest that while the afferent pathways to light are still open during sleep, the degree of responsiveness is considerably reduced as compared with the waking state. Furthermore, diminution in responsiveness becomes more evident as sleep deepens. The present investigations give no clue to the level (cortical or subcortical) at which this reduction in response takes place.

The interpretation of the data obtained in light sensitive epileptic patients is difficult because the precise mechanisms and pathways involved in the epileptic discharge remain conjectural, even in the waking state. It is generally supposed that the spike and wave type of discharge originates in, or at least is regulated from, a subcortical level. It is known that this discharge often occurs with greater frequency during sleep, which is itself probably regulated from subcortical levels. The photoconvulsive type of response probably results from some abnormal leakage in the optic system so that the spike and wave initiating center becomes activated by light impulses (figure 4). It will be remembered that 43 per cent of our light sensitive patients lost their light sensitivity during sleep, and that the patients with the most marked degree of light sensitivity in the waking state were those most likely to retain their response during sleep. This indicates that the onset of sleep is associated with an elevation of threshold at some point in the photoconvulsive system. Since the diminution of light sensitivity was not constantly associated with reduction in the spontaneous spike and wave activity (in fact, often the reverse situation was encountered), it seems unlikely that the increase in the threshold occurs either in the "spike and wave center" or at the terminal neurons of the cortex. This would leave the "leakage pathway" between the lateral geniculate body and the "spike and wave center" as the most likely site for the increase in threshold during sleep. Since in previous studies

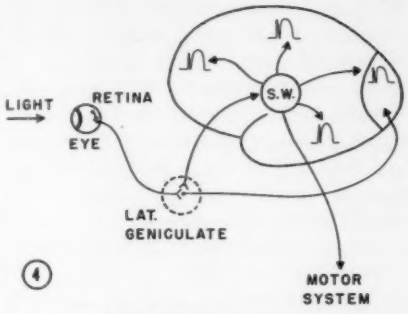

FIG. 4. Hypothetical pathway involved in photoepilepsy.

Bickford[15] demonstrated that barbiturates may raise the convulsive threshold to light even in the waking state and we have demonstrated in this study that the barbiturates are capable of adding to the spontaneous elevation of seizure threshold in sleep, the point of action of barbiturates presumably also would be on this pathway.

The over-all similarity in reduction of responsiveness to light in normal and epileptic patients in spite of different final mechanisms raises the question as to whether the rise in the threshold could take place at a point in the optic system that is common to both types of responses. This might involve the retina, optic nerve, or the lateral geniculate body. Possibly the elevation of threshold might be attributed to a change in the position of the eyeballs plus pupillary constriction during sleep, producing a decrease in the amount of light reaching the retina. This explanation is unlikely since the light stimulus is supramaximal in intensity and light appears to reach the retina of the closed eye by transmission through the sclera. Since light stimulation was in most instances carried out under reduced illumination in the room during sleep, this would cause an increase in the degree of dark adaptation present at the time of stimulation as compared with the waking state. However, observations made on waking patients suggest that the light response usually increased with diminution of surrounding illumination so that this factor may be supposed, other things being equal, to lower the threshold under conditions of sleep stimulation. Therefore it seems unlikely that loss of responsiveness is retinal in origin. Changes in the optic nerve relative to sleep can probably be excluded on general grounds. With regard to the lateral geniculate body, Chang[16] has recently shown in animals that increasing retinal illumination caused an increase in response to concomitant light stimulation. This effect originates in the geniculate. While this effect is in the right direction to account for diminution of light response when carried out under reduced general illumination, this could not be demonstrated in the human being under conditions of light stimulation employed in these experiments. We are still left with the possibility that sleep per se influences the light response threshold at the lateral geniculate body. While there is no direct evidence of a change in the light threshold at the lateral geniculate body, animal experiments carried out by Bickford[17] disclosed a change in the spontaneous electrical activity of this structure during sleep which could at least provide a basis for the required change in threshold. We may conclude that the rise in threshold in the optic pathways associated with sleep probably occurs at the geniculate level, since this is the last point of the pathway which is common to both the normal photic response as well as the photoconvulsive responses.

SUMMARY

The photic responses of five normal persons were investigated electroencephalographically during sleep. Photic responses were observed in all instances by means of automatic low frequency analysis. The responses tended to decrease with the deepening of sleep.

Next, the effect of light stimulation on 30 epileptic patients sensitive to light and 46 who were not sensitive to light was investigated during sleep. The sensitivity to light tended to be unchanged,

reduced, or absent during sleep. The responsible factors seem to be the severity of the pathologic process and the effect of premedication necessary to induce sleep in some cases. Patients severely sensitive to light tended to remain light sensitive to the same degree in spontaneous sleep, while in medicated sleep a reduction or absence of these pathologic responses occurred. Patients mildly sensitive to light lost their light sensitivity even in spontaneous sleep. In no instance did sensitivity to light increase compared with that in the waking state. None of the 46 epileptic patients who were insensitive to light in the waking state became sensitive to it during sleep.

Seizure discharges in the electroencephalogram which produced clinical manifestations in the waking state became less effective in producing outward signs during sleep.

In two cases focal occipital sharp waves could be triggered by the flashing light during the waking state and during sleep.

The optic pathways to the cortex apparently remain patent during sleep although the threshold to stimuli rises. This rise in threshold may occur at the level of the lateral geniculate body.

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Hypothalamic Tumor

Correlation between Symptomatology, Regional Anatomy, and Neurosecretion

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INFORMATION may sometimes be obtained from the study of human pathologic material which not only furnishes data concerning disease processes but also supplements physiologic knowledge derived from animal experimentation. When nature chances to make a lesion more discrete than is generally possible by experimental technics, this provides observations regarding the morphologic basis of disordered function not otherwise obtainable. In a region such as the hypothalamus, where a great number of functionally separate elements are confined in a small space, the occurrence of such lesions is unfortunately rare, so that most of our knowledge of this region comes from the laboratory. We have been able to study the clinical course and autopsy material of a patient with a uniquely localized hypothalamic lesion, allowing inferences regarding anatomy and functional localization.

In addition, it has furnished an opportunity to apply to the study of such cases a staining technic which has shown itself to be of particular value in the histologic demonstration of certain structures in the region of the hypothalamus and pituitary. With the application of the chrome-alum-hematoxylin and phloxine stain of Gomori,[1] contributions have recently been made to our understanding of the site of origin of the hormones of the posterior pituitary.[2,3] This technic selectively stains a granular and colloidal substance found in the supraoptic and paraventricular neurons, along their axons, and in the neurohypophysis, especially the posterior lobe of the pituitary where it forms dense aggregates. It is believed that the substance, referred to as neurosecretory material, is formed in the neurons of the above mentioned nuclei, transported along their axis cylinders, and deposited in the neural lobe of the pituitary where it is stored and released as needed. That the stainable material represents the posterior lobe hormone, or is closely associated with it as a carrier-substance, is rendered likely by the fact that significant titers of this hormone are present in all the tissues where neurosecretory material is demonstrable, but not elsewhere.[4] Furthermore, the stainable material is quickly released from the neurohypophysis following a noxious stimulus,[5] a circumstance under which the antidiuretic hormone is known to be secreted.[6] In addition, the material

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gradually disappears from the pituitary when the demand for antidiuretic hormone is maintained at a high level by chronic dehydration.[7,8,9]

Two cases of hypothalamic tumor are presented with a seemingly paradoxic relationship between the size and location of the tumor and the resulting symptomatology. One patient suffered from severe diabetes insipidus and associated neuroendocrine disturbances, and at autopsy showed a minute tumor of the median eminence of the tuber cinereum too small to be seen on inspection of the specimen with the naked eye. The other showed a large tumor destroying or displacing the entire hypothalamus, but without any clinical evidence of disturbed water metabolism. Study of neurosecretory material with the Gomori stain showed in the first case the complete absence of secretory neurons in the otherwise intact hypothalamus, with the corresponding absence of neurosecretory material in the neurohypophysis. Examination of the second case demonstrated persistence of granule-bearing secretory neurons displaced far from their accustomed location, but viable and functionally intact, while the neurohypophysis showed normal amounts of neurosecretory material in some locations, with the material reduced or absent in others. A third case of traumatic death was examined and illustrated as an example of the normal neurosecretory morphology, a subject which has already received thorough study in animals[10,11] and man.[12]

The microscopic findings tend to resolve the seeming paradox in symptomatology and at the same time lend credence to the theory that the neurosecretory material bears an intimate relationship to the antidiuretic principle of the posterior pituitary. In the case of the tumor of the median eminence, the lesion is so unusually well confined to this structure that it allows anatomic study of the effects of such a lesion on neighboring structures of the hypothalamus, pituitary, and stalk, without the disturbing effects of tumor encroachment, impairment of the vascular supply, or direct surgical intervention.

CASE REPORTS

Case 1.—A 14 year old boy was admitted to the Montreal Neurological Institute on January 12, 1953 complaining of headaches, polyuria, and polydipsia. His illness had begun 18 months prior to admission when it was observed that he was voiding large amounts of urine and drinking unusual quantities of water. Approximately six months after the onset, a diagnosis of diabetes insipidus was made and the symptoms effectively controlled by nasal insufflation of pituitary powder.

He was well until two weeks before admission when he began to have nausea and headaches which were severe and occurred daily. There were occasional episodes of diplopia during this same period. Family history and past history were noncontributory. At the time of admission the patient appeared normal in height and weight, but his body was immature, with absence of pubic and axillary hair, undescended testes, and infantile external genitalia. Early papilledema was present bilaterally. There was paresis of the left third and sixth cranial nerves. The visual fields were full and the remainder of the neurologic examination was normal.

A ventriculogram was done on the day of admission. This showed a smooth-surfaced tumor in the posterior half of the third ventricle which had completely obstructed the aqueduct of Sylvius, causing a marked internal hydrocephalus. The lesion infiltrated the posterior half of the left thalamus and basal ganglia. A presumptive diagnosis of pinealoma was made, and on the same day a ventriculoperitoneostomy was performed. For a day after operation he was alert and rational and free of headache. His diabetes insipidus was aggravated, with the patient asking almost continually for water and voiding large amounts of urine with a low spe-

cific gravity (1.002). On the second postoperative day he again had headache and was drowsy and at times irrational. It was evident that the ventriculoperitoneostomy was not functioning, so the cranial end of the tube was relocated.

Following this procedure the patient's condition was satisfactory with the diabetes being controlled with nasal pituitrin. Appropriate tests showed that the ventriculoperitoneostomy was functioning. On January 14, 1953, deep x-ray therapy was started. Except for poor appetite and occasional periods of nausea, he remained well until February 9, 1953 when he developed a fever accompanied by nausea, vomiting, and drowsiness. Fluid obtained from the tube and the ventricles was cloudy, containing many leukocytes and gram positive cocci, identified on culture as *Staphylococcus pyogenes*. He was treated with intraventricular and oral chloramphenicol, but cultures of the cerebrospinal fluid remained positive until intraventricular Bacitracin was substituted for the chloramphenicol.

After the onset of this infection the patient did poorly. His oral intake of food and liquids was extremely low and nutrition had to be maintained by gastric feedings. However, unless he was given the pituitrin regularly the urinary output would still be high with low specific gravity. He had frequent periods of drowsiness and confusion as well as occasional hallucinatory states. He lay quietly in bed, taking little interest in his surroundings, but could often answer questions intelligently. X-ray therapy was discontinued after a minimal tumor dose of 2,464 r in 24 days. A ventriculogram was done on March 10, 1953 and there was now no evidence of tumor. However, there was a suggestion of a space-occupying lesion in the posterior part of the right lateral ventricle completely occluding the temporal horn. The ventriculoperitoneostomy tube was removed and when the tube was withdrawn there was a collection of purulent material at the end of the cranial portion. Although several exploratory needle punctures were made in the right temporal region, no abscess was found.

Up to the time of death he failed to improve, remaining listless, drowsy, and complaining of excessive fatigue. Finally he refused food and fluids, and although he was given gastric feedings he remained chronically dehydrated with constant high blood sodium and low potassium, the latter not correctable by a high potassium diet. He continued to deteriorate and died on April 9, 1953.

Laboratory data: January 12, 1953. Urinalysis: specific gravity 1.002, neutral; albumin and sugar, negative. Ventricular fluid clear, no cells, Pandy 0, protein 10 mg. per cent. January 17, 1953. Hemoglobin 52 per cent. February 2, 1953. Hemoglobin 68 per cent. February 9, 1953. Ventricular fluid cloudy. 112 white cells per cubic millimeter. February 10, 1953. Hemoglobin 72 per cent. February 18, 1953. Hemoglobin 80 per cent, red cells 4.2 million. March 10, 1953. Ventricular fluid clear, Pandy 1 plus, protein 166 mg. per cent. March 13, 1953. Blood chemistry: serum sodium 168 mEq/L; serum potassium 3.4 mEq/L; chlorides 116 mEq/L. March 20, 1953. Hemoglobin 72 per cent; hematocrit 22 per cent. Blood chemistry: serum sodium 168 mEq/L; serum potassium 3.7 mEq/L; serum chlorides 121 mEq/L; NPN 20 mg. per cent. April 6, 1953. Lumbar cerebrospinal fluid clear, colorless, pressure 70 mm. water. 18 white cells per cubic millimeter, Pandy 2 plus, protein 456 mg. per cent.

Postmortem examination. The body was that of a poorly nourished boy of 14, appearing younger than the stated age. Examination of the thoracic and abdominal viscera failed to reveal any significant abnormality.

Except for some thickening of the basal leptomeninges and a small opening in the right posterior parietal region, the brain was not remarkable. The hypothalamus and pituitary were removed as a block for separate fixation. After cutting the brain in the coronal plane, the lateral and third ventricles were found to be moderately dilated, while the aqueduct and fourth ventricle were only slightly dilated. The occipital and temporal horns of the right lateral ventricle were filled with an abscess. The pineal body was slightly enlarged. Extending anteriorly from the pineal gland a tumor entered both thalami and involved the massa intermedia. Grossly, the hypothalamus and pituitary appeared normal.

Microscopic examination: Sections were made through the pineal, and through the mid- and posterior portions of the tumor in the thalami. These were stained with hematoxylin and eosin, cresyl violet, hematoxylin and Van Giesen, and Mallory's phosphotungstic acid and hematoxy-

FIG. 1. Tubular structure in tumor from case 1 taken from the thalamic region, showing mucus-bearing lining epithelium. Hematoxylin and eosin stain.

lin. The entire hypothalamus was imbedded as a single block and serial sections were cut coronally and stained with Gomori's chrome-alum-hematoxylin and phloxine, and cresyl violet. Other sections of the hypothalamus, not taken serially but through representative portions of the lesion, were stained with hematoxylin and eosin and Masson's trichrome method. The pituitary was separated from the hypothalamus, sectioned serially in the sagittal plane, and stained in the same manner as the hypothalamus.

The tumor in the thalami was composed principally of round, oval, and flattened spaces lined with a ciliated columnar or cuboidal epithelium (figure 1). These cells contained large, elongated, densely chromatic nuclei. In many instances, the cytoplasm bulged in toward the lumen of the adjacent cavity and contained a clear, spherical inclusion. Mucin could be stained within these cells and they resembled the goblet cells of respiratory epithelium. Most of the tissue between the tubular structures was arranged loosely containing here and there bi- and multipolar cells resembling primitive neuroglia. There were a few small areas containing sheets of cells, believed to be the above-described structures sectioned tangentially.

This tumor was continuous with the pineal body, although only a localized portion of this structure contained the neoplasm just described. There was, however, no recognizably normal pineal tissue, the body consisting of many corpora aranacae, between which there were bands of collagenous connective tissue and amorphous material. In the median plane of the third ventricular floor was a small, elongated, and rather

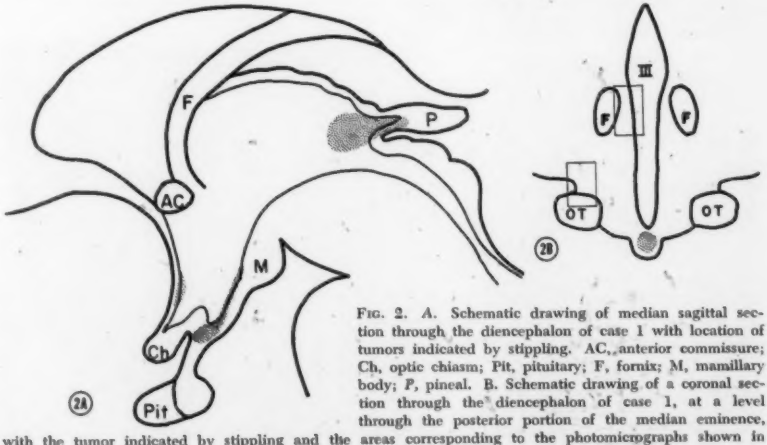


FIG. 2. *A.* Schematic drawing of median sagittal section through the diencephalon of case 1 with location of tumors indicated by stippling. AC, anterior commissure; Ch, optic chiasm; Pit, pituitary; F, fornix; M, mamillary body; *P*, pineal. B. Schematic drawing of a coronal section through the diencephalon of case 1, at a level through the posterior portion of the median eminence, areas corresponding to the photomicrographs shown in figures 6 and 7 outlined by the rectangles. OT, optic tract; F, fornix; III, third ventricle.

circumscribed mass of tumor, the limits of which are depicted in figures 2 and 3. In this location the tumor was moderately cellular and pleomorphic, there being no discernible pattern and no completely characteristic cell type (figure 4). In the central portion of the tumor were cells with small round or oval hyperchromatic nuceli and almost no cytoplasm. They were loosely arranged in an ill-defined and fragmented stroma. In this same region were scattered multinucleated giant cells and a few blood vessels, most of which possessed thick, collagenous walls. A second type of cell was also seen, particularly around the periphery, where the increased concentration of such cells gave the tumor a ring-like appearance under low power (figure 3). These cells had fairly large oval or elongated nuclei with their cytoplasm arranged in a sheet or in multiple tapering processes. At the very margin of the tumor, such cells could be seen invading the adjacent brain tissue with long processes radiating out perpendicular to the tumor border. They appeared to be of neuroglial origin, with many of them resembling polar spongioblasts.

This tumor must have been profoundly affected by the x-ray treatment given, judging from the marked decrease in size shown on successive air studies. The picture presented by the tuberal implant may be interpreted as showing widespread degenerative changes in the central portions of the tumor secondary to the irradiation, with destruction of many tumor cells, disruption of the stroma, and infiltration by hematogenous elements. At the periphery, in contrast, were concentrated invasive neoplastic cells, apparently proliferating spongioblasts.

A second implant, smaller than that just described but similar in microscopic appearance, was found attached to the lamina terminalis. There was no extension down the pituitary stalk and serial sections of the pituitary itself

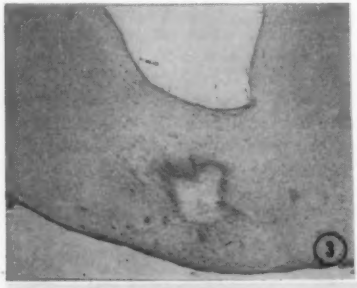
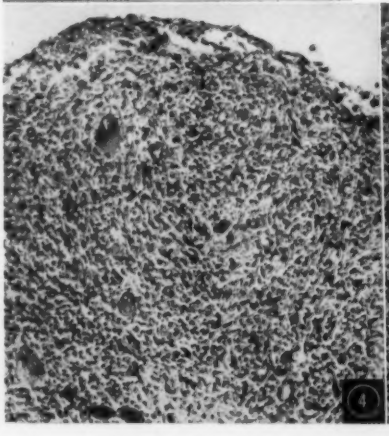


FIG. 3. Coronal section of the ventricular floor posterior to the median eminence with the small mass of the tumor centrally placed. Cresyl violet stain.

FIG. 4. Section through the tumor in case 1, at a point more posterior to figure 3, where the lesion protrudes slightly into the ventricle. Degenerative changes consequent to radiotherapy are seen. Hematoxylin and eosin stain.

FIG. 5. Low power photomicrograph through the pituitary of case 1, who had diabetes insipidus, including posterior lobe and adjacent portion of the anterior lobe. The posterior lobe is atrophic and free of any tumor invasion. Gomori stain.



showed no tumor, the anterior lobe appearing normal and the neural lobe small and shrunken (figure 5).

Case 2.—A 14 year old boy was admitted to the Montreal Neurological Institute on August 10, 1951 complaining of headaches and blurring of vision. He had first had headaches two years previously, associated with a sense of pressure over the vertex. All this improved gradually, and he was well again until seven months before admission when the headaches recurred but were relieved by glasses. In June 1951 the headaches reappeared and medical examination at that time was reported to be negative; one month later, the headaches became persistent. There was a sudden episode of blurring of vision two weeks before admission, with some vomiting. A few days before coming into the hospital he yawned frequently in an attempt to relieve the sense of pressure in his head, and on the day before admission he became unsteady when standing or attempting to walk. The family history was non-contributory. The past history showed that at the age of eight years he had been given glasses for "poor vision."

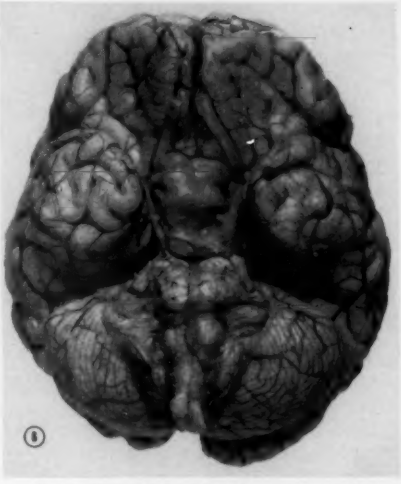


FIG. 6. Base of the brain in case 2, showing replacement of the hypothalamus with tumor mass.

Examination showed a well-nourished and normally developed boy of 14. The optic disks were pale, particularly the left, and there was a left incongruous homonymous hemianopsia. Chaddock's sign was present bilaterally, and an Oppenheim's sign on the right. Roentgenograms of the skull gave evidence of increased intracranial pressure as manifested by pressure atrophy of the dorsum sellae. A ventriculogram was done on August 17, 1951. This showed a lesion obstructing the foramina of Munro, the right more than the left, causing relative enlargement of the right lateral ventricle. There seemed to be swelling of the left thalamus.

On August 17, 1951 a right frontal craniotomy was done and the third ventricle explored through the corpus callosum. A neoplasm was found occupying the anterior floor of the third ventricle and small portions of the tumor were removed. After this procedure the patient had many generalized convulsions. He was febrile, drowsy, and irritable. Because the intracranial pressure remained high a bilateral ventriculocisternostomy was performed on August 21, 1951. He did not improve and gradually became unresponsive. He then began to have frequent spasms of extensor rigidity associated with sweating on the left side of the face and an increase in skin temperature on the left side of the body. He died on October 20, 1951.

Laboratory data: August 13, 1951. Hemogram red cell count 5 million, hemoglobin 100 per cent, white cells 5,200, a slight increase in the sedimentation rate, moderate neutropenia, and slight lymphocytosis. August 17, 1951. Ventricular fluid, Pandy negative, proteins 12 mg. per cent. August 25, 1951. Hemoglobin 72 per cent. September 18, 1951. Hemoglobin 77 per cent, white cell count 13,900.

Postmortem examination: At autopsy, the body was emaciated but otherwise normal in size and appearance. There was a healed right frontal craniotomy wound and a more recent suboccipital craniectomy wound. The dura was adherent to the parietal bone flap, and both ventriculocisternostomy tubes were in place.

The cerebral gyri were flattened and the intervening sulci partly obliterated. The anterior portion of the corpus callosum contained a small 1 cm. hole which entered the third ventricle. The entire floor of the third ventricle between the septal region anteriorly and the cerebral peduncles posteriorly had been replaced by an irregular tumor mass (figure 6). The tumor displaced the gyri recti anteriorly,

the olfactory trigones anteriorly and laterally, the unci laterally, and had stretched apart the cerebral peduncles. The optic nerves, chiasm, and both internal carotid arteries had been surrounded by tumor and could not be identified. The left third nerve was imbedded within the tumor, and the pituitary stalk was flattened to a thin band and displaced to the right.

After the brain had been sectioned in the coronal plane, the lateral ventricles were found to be widely and symmetrically dilated. The right foramen of Munro was dilated, while the left was occluded by tumor tissue. A large, lobulated tumor mass almost filled the third ventricle, reducing the lumen to a slit anterosuperiorly. The basal ganglia and anterior thalami were displaced laterally. In the gross specimen, the hypothalamus seemed to be entirely destroyed. The tumor had a grayish, gelatinous, semitranslucent appearance with a few small cystic spaces. It was firm in consistency before as well as after fixation in 10 per cent formalin.

Microscopic examination: Sections of the tumor were stained with hematoxylin and eosin, hematoxylin and Van Giesen, Mallory's phosphotungstic acid and hematoxylin, and frozen sections were impregnated with gold and silver. The pituitary and sections through the hypothalamus were stained in addition with Gomori's chrome-alum-hematoxylin and phloxine. The neoplasm was sparsely cellular. The tumor cell nuclei were uniform in size and shape with abundant chromatin granules. The cytoplasm was arranged in processes with some cells being unipolar, others bi- or multipolar. Glial fibrils were seen within these cytoplasmic processes. The cells tended to be oriented in a parallel manner. Blood vessels were not conspicuous, but sometimes showed a tortuous course or formed loops and glomerulus-like formations surrounded by a delicate reticulin network. In the metallic preparations there were bundles and interlacing streams of fibrils.

The brain was compressed but not invaded by the neoplasm and intact neurons belonging to the supraoptic or paraventricular nuclei could be identified adjacent to the tumor.

DISCUSSION

A large number of reports of the autopsy material in cases of diabetes insipidus is available in the literature. In the largest single series,[13] a wealth of pathologic findings is presented, but the nature and location of the lesions were so varied that the author felt no one theory of etiology of the disease was supported more than any other. The subject was reviewed again in the monograph of Fisher, Ingram, and Ranson,[14] in which they felt that most of the clinical evidence was compatible with their proposition that the disease is caused by interference with the supraopticohypophysial system. This concept is now generally accepted and no evidence to the contrary has been subsequently forthcoming. In most of the autopsy reports published on diabetes insipidus, the lesion was too large or diffuse to permit careful histologic examination of the surrounding structures. Exceptions to this may be found, however, in certain well-studied cases, including those of Lehrmitte,[15] Stringer,[16] and others.[17–20]

Anatomic Considerations

The lesion in case 1 was so placed that it destroyed the median eminence of the tuber cinereum and at the same time divorced the infundibular stem and process from the hypothalamus, thus eliminating all of the neural connections between the hypothalamic nuclei and the neurohypophysis (figure 2). The lesion was confined almost exclusively to the median eminence, with a small subependymal tail extending posteriorly in the midline to the mammillary recess. The primary tumor was at some distance in the posterosuperior wall of the third ventricle with some extension into the adjacent thalamus and pineal, and a second smaller implant was present in the lamina terminalis.

Serial sections of the hypothalamus were examined, particular attention be-

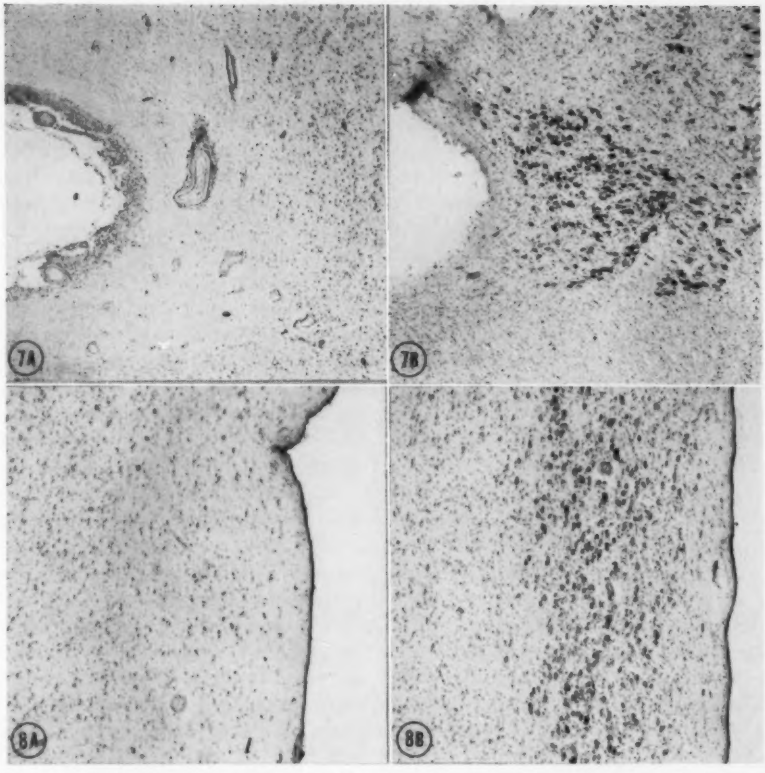


FIG. 7. *A.* Section through one supraoptic nucleus of case 1, corresponding to the region outlined by the lower rectangle in figure 2B. No supraoptic neurons are seen. Cresyl violet stain. *B.* Section through the same region in normal human brain, showing intact supraoptic nucleus. Cresyl violet stain.

FIG. 8. *A.* Section through one paraventricular nucleus of case 1, corresponding to the region outlined by the upper rectangle in figure 2B. No paraventricular neurons are seen. Cresyl violet stain. *B.* Section through the same region in normal human brain, showing intact paraventricular nucleus. Cresyl violet stain.

ing paid to the constituent nuclei and their degree of preservation. The supraoptic and paraventricular nuclei were, for all practical purposes, completely degenerated (figures 7 and 8); that is, no neurons showing the characteristic normal morphology of these cells were observed. Additional check was possible by employing the Gomori stain on all the sections. The supraoptic and paraventricular neurons stain selectively with this stain because of the presence of secretory granules in their cytoplasm. In the case under consideration no granule-bearing neurons were seen. That the principle if not the only projection of the supraoptic nucleus is via the supraopticohypophysial tract to the neurohypophysis has been suspected ever since Greving first described the tract which now bears his name.[21] Thus the proportion of supraoptic neurons surviv-

ing after amputation of the neurohypophysis is low if the lesion is made proximally, ranging from 14 per cent to 20 per cent in certain species,[22,23] and even lower – 0 to 9 per cent – if the median eminence is injured in addition.[23,24] In a single case of stalk section in man,[25] the supraoptic nuclei were reduced to 15 per cent of normal five months after the operation. The high degree of cell loss, in our case approaching 100 per cent, is understandable when one considers the completeness of the lesion and the long survival period (21 months after the onset of diabetes insipidus).

By comparison, the projection pathways of the paraventricular nuclei are not so well understood. Although it seems likely that at least some of these cells project to the neurohypophysis, the proportion of neurons degenerating after stalk section is somewhat less than is observed in the supraoptic nucleus. In a series of hypophysectomized rats, only 35 per cent cell loss was reported,[26] and in the monkey, only 20 per cent after stalk section.[23] Only slight atrophy was described in dogs and cats after stalk section,[24] but it was mentioned that there may be greater loss of cells following lesions of the median eminence in dog and man. In the case of human stalk section, the authors described some degeneration of the paraventricular nuclei but were uncertain as to its extent.[25] Following supraopticohypophysial tract section in the dog, well marked atrophy and cell loss in both supraoptic and paraventricular nuclei was found.[27] O'Connor[22] reinvestigated the problem in 1947; by making proximally-placed lesions and using rigid criteria in identifying paraventricular neurons, he found only 20 per cent of the cells surviving after bilateral tract section in dogs, and he concluded that the paraventricular nucleus projects principally, if not exclusively, to the neurohypophysis. More recently, Laqueur,[28] making use of the Gomori stain which selectively delineates the secretion-bearing axons of the paraventricular cells, was able to trace a variety of efferent pathways from the paraventricular nucleus all of which seemed to lead eventually to the neurohypophysis, some passing there directly, many sweeping by the supraoptic nucleus, and a few passing as far laterally as the internal capsule before turning medially.

Varying degrees of retrograde degeneration of the paraventricular nuclei following lesions of the tuber cinereum have been mentioned in several case reports.[12,17] In our own case, the high degree of cell loss from the paraventricular nuclei, again approaching 100 per cent by both Nissl and Gomori stains, suggests that the principal or sole destination of paraventricular fibers in man is the neurohypophysis. Opinion to the contrary has been expressed, however,[20] in the report of a case in which cystic lesions destroyed both supraoptic nuclei, and in which both paraventricular nuclei had undergone degeneration. The lesions in this case were rather extensive, including both supraoptic regions and the anterolateral walls of the infundibulum and median eminence, thus occupying most if not all of the region through which the paraventriculohypophysial tract, as we now understand it, must pass on its way to the neurohypophysis.

A third nuclear group showing conspicuous cell loss in our case was that group of neurons which surrounds the most proximal portion of the neurohypophysis (the median eminence). Following recent detailed anatomic consid-

eration in the cat[29] and man,[30] it has been termed the nucleus infundibularis, and corresponds at least partly to the noyaux propres du tuber,[15] the noyau periventriculaire infundibulaire,[31] the nucleus arcuatus,[32] nucleus periventricularis arcuatus,[33] and the median infundibular and median arcuate.[34] This nucleus is a rather distinct entity, and not to be confused with the ventromedial nucleus or the lateral tuberal nuclei which were quite intact in our case. Because the posterior and lateral limits of this nucleus are poorly defined, the exact degree of cell loss is difficult to estimate, but seemed to be well over half. Since these neurons are Gomori-negative, this stain gave no special information. These findings would support the theory of Spatz[35] and his group who hold that the nucleus infundibularis is intimately connected with the neurohypophysis. They ascribe to it an afferent role, but the retrograde degeneration of this nucleus after destruction of the median eminence is more in favor of an efferent function, since this sort of degeneration commonly follows section of axons but is not known to follow interruption of dendrites.

Examination of the other constituent nuclei of the hypothalamus revealed no clearcut abnormalities. Blockage of the aqueduct by tumor before the institution of the ventriculoperitoneostomy resulted in some degree of internal hydrocephalus with ballooning of the lamina terminalis and thinning of the adjacent third ventricular wall, making examination of the preoptic region unsatisfactory. The anterior hypothalamic area, ventromedial and dorsomedial nuclei, posterior hypothalamic area, lateral hypothalamic area, and mammillary nuclei all appeared intact. The lateral tuberal nuclei were present but not well developed.

The stalk and neural lobe of the pituitary were shrunken and atrophied (figure 5). The tissue was much more densely cellular than the normal, containing large numbers of pituicytes and some blood vessels. This was interpreted as due to loss of the nervous parenchyma of the tissue and consequent condensation of the supporting elements

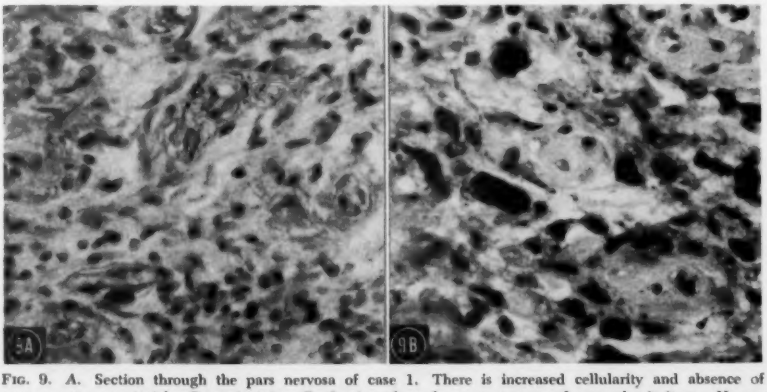


FIG. 9. *A*. Section through the pars nervosa of case 1. There is increased cellularity and absence of neurosecretory material. Gomori stain. *B*. Section through pars nervosa of normal pituitary. Neurosecretory material is present as colloidal masses and scattered granules. Gomori stain.

of the stroma, in particular the pituicytes, and was similar in all respects to the findings of Fisher and his co-workers[14] in cats with experimental diabetes insipidus. Sections stained by the Gomori method showed almost complete absence of neurosecretory material (figure 9). With the exception of two small foci containing five or six darkly staining granules, none of the characteristic granular or colloidal substance was to be seen, and the pituicytes, instead of being widely separated by neurosecretion-filled vesicles of varying sizes, lay side by side often in parallel streams or sheets. The histologic appearance of the anterior pituitary was not remarkable.

Physiologic Considerations

An attempt to correlate the symptoms and signs of case 1 with the anatomic findings just described is desirable in view of the discreteness of the lesion and its rather unequivocal effects. Although he was 14 years old, this patient showed no evidence of the onset of puberty. A wide range of normal is described,[36] but the proportion of normal males with no evidence of puberty by 14 is small. Disturbances in the sexual sphere from lesions of the hypophysial and hypothalamic regions have been recognized ever since Fröhlich's[37] first case report. It is now clear that any lesion which destroys the pituitary will eliminate this source of gonadotropin, with resulting infantilism or sexual dystrophy. Lesions of the hypothalamus may have a similar effect, however, without attendant panhypopituitarism of any marked degree, and it is now possible to postulate the existence of a hypothalamic mechanism which controls the pituitary's output of gonadotropin. Impairment of this mechanism results in delayed or absent puberty in the young individual, and amenorrhea and varying degrees of hypogonadism in the adult. Early destruction of influences which normally inhibit this mechanism may result in precocious puberty.[38]

The anatomic substrate for such a mechanism must include the median eminence, since its experimental destruction results in gonadal atrophy,[39–41] and also the pituitary stalk, since oestrus cycles in the rat are abolished by its section provided that regeneration of the hypophysial-portal vessels is prevented.[42] Transmission of a humoral stimulus from the median eminence to the anterior pituitary by way of the hypophysial-portal vessels has been postulated[43] and may involve the release of both adrenergic and cholinergic components.[44]

Experimenting directly upon the hypothalamus, Dey produced a disturbance in the estrus cycle of the guinea pig by making large lesions in both anterior hypothalamic areas,[39] and a similar disturbance was produced in the rat by Hillarp[45] either by making smaller lesions in the anterior hypothalamic area or with superficial lesions just posterior to the paraventricular nucleus on each side with the latter site believed to represent interruption of the fiber tract going to the pituitary stalk. Harris[46] has produced ovulation by direct stimulation of the anterior wall of the tuber cinereum just above the anterior part of the median eminence in the rabbit. On the basis of experimental and clinical observations, Spatz and his co-workers[35] consider the parvocellular region of the tuber cinereum to be the hypothalamic sexual center, although their opinion of its efferent pathway differs from that of Harris.

In the present case, the sexual infantilism may be attributed to destruction of the median eminence. Degeneration of the supraoptic and paraventricular nuclei is related to the disturbance in water metabolism and no connection between these nuclei and gonadal function has been demonstrated. The anterior hypothalamic area, destruction of which produces constant estrus, was intact in our case. The degeneration of the nucleus infundibularis in the first case is of particular interest, however, since this nucleus is regarded as the hypothalamic sexual center by Spatz, and stimulation in the region of its anterior portion produces ovulation.[46] In comparing results of experimental work in animals with the pathologic findings in man, it should be kept in mind that the nucleus infundibularis surrounds the median eminence (infundibulum) in most mammals, but shifts to a position largely lateral and posterior to it in primates, consequent to the anterior rotation of the pituitary stalk.[30]

Obesity is generally associated with Fröhlich's syndrome, but does not necessarily accompany all lesions of this region, as illustrated by the first case who was normal in weight, stature, and bodily appearance, although immature. Recent experiments in the rat implicate lesions in the region of the ventromedial nucleus of the hypothalamus or the region just lateral to this nucleus as the source of hypothalamic obesity,[47] attributing to these regions an inhibitory influence on a more laterally placed "feeding center." In the case under discussion, the ventromedial nuclei were quite intact as well as the area surrounding them, accounting, we believe, for the absence of clinical obesity or hyperphagia.

The diabetes insipidus is accounted for by the lesion interrupting the supraoptico- and paraventriculohypophysial tracts bilaterally as they converge into the median eminence. Of some interest is the persistently elevated serum sodium and chloride and the depressed serum potassium, which were manifest during the latter phases of the disease. These features are not generally associated with diabetes insipidus, particularly when water intake is not restricted and Pitressin given regularly, as they were in our case. Also noteworthy was the complete absence of thirst during the last two months of the illness. During this period he was still alert enough to obstruct willfully attempts to hydrate him by oral feedings, gavage, or parenteral fluids. He never requested fluids spontaneously and refused them when they were offered, despite dryness of the lips and oral mucous membranes and elevated serum electrolytes.

Similar distortion of the serum electrolyte pattern has been reported in a variety of cases of intracranial disease,[48] when it is sometimes due to inadequate water intake in the comatose patient. Insufficient water intake may have played some role in our case, although consciousness was only mildly impaired at the time the determinations were made. Aberration of central mechanisms controlling serum electrolytes has also been suggested in cases of this sort[48,49] with implication of the hypothalamus and its contained osmoreceptors.[6] These receptors are connected to, if not identical with, the supraoptic and paraventricular neurons. Since these neurons were degenerated in the present case, central appreciation of the concentration of serum electrolytes may have been seriously impaired, and this would further

contribute to the electrolyte imbalance. This particular pattern of electrolyte disturbance has been shown to be due to still other causes, however,[48,49] in which the apparent absence of diabetes insipidus suggests relative sparing of the supraopticohypophysial system. We have encountered such cases clinically, especially following head injury, one of which showed a serum sodium in excess of 180 mEq/L.

Whether one is justified in going further in an attempt to correlate the lack of spontaneous thirst with the absence of the supraoptic and paraventricular nuclei is questionable, since the patient's general condition was deteriorating when the thirst disappeared and since diabetes insipidus is generally characterized by normal or increased thirst. Studies have recently been reported, however, on a similar case showing chronic hyperosmolarity of the body fluids, diabetes insipidus, and anterior pituitary insufficiency, in which a derangement of the thirst mechanism was postulated.[50] Furthermore, it is possible to induce thirst experimentally by injecting minute quantities of hypertonic saline directly into the region of the supraoptic nucleus in goats,[51] suggesting that hypertonicity in this area activates one of the mechanisms by which thirst reaches consciousness.

Clinical evidence of adrenal dysfunction was not noted in our case with diabetes insipidus, although detailed tests were not carried out. The adrenals appeared normal at autopsy and sections of each adrenal were made and stained with Sudan III and Oil Red O, in addition to the routine chromatic stains. Histologically, the glands appeared normal, with the medulla and the three zones of the cortex clearly defined and well preserved. Examination of the sections stained for lipids showed large amounts of intracellular sudanophilic material deposited throughout the cortex, with the exception of a few scattered foci in the zona glomerulosa, where the quantity of lipid was reduced. The cortex was uniform in appearance and averaged about 0.9 mm. in thickness. Taking into account the patient's youth (age 14) and the absence of any hormone therapy except Pitressin, this is the picture one might expect in the adrenals of an individual dying from sudden trauma or a very brief illness. The last two months of his illness were punctuated, however, by two major surgical procedures, a course of x-ray irradiation, and subsequently meningitis and ventriculitis. During the final month of his illness, the x-ray treatments were discontinued and the meningitis and ventriculitis controlled with antibiotics, but he still presented a problem in fluid and electrolyte balance and nutrition, and a temporal lobe abscess was present, as revealed at autopsy.

It seems clear then that the patient was subjected to a series of potent alarming stimuli, any one of which might be expected to activate the pituitary-adrenal axis with resulting lipid depletion of the adrenal cortex for a time at least, and that at least some of these factors were still acting up to the time of death. What one should expect in the histologic picture of the adrenal after chronic or multiple illness is still a matter of controversy, but some degree of lipid depletion is the rule,[52,53] whereas the present case showed little or none. A similar situation has been produced experimentally by Laqueur and co-workers,[41] in which lesions of the infundibular region in cats resulted in diabetes insipidus,

gonadal atrophy, and impairment of the hypothalamic control of the ACTH response to stress, as evidenced by decreased eosinopenic response to epinephrine or laparotomy, and an accumulation of lipids in the outer fascicular zone of the adrenals, in contrast to a loss of lipids in animals with lesions elsewhere. The resemblance in symptomatology between these experimental animals and case 1 is striking, and the possibility must be considered that the absence of adrenal lipid depletion in the present case, despite a prolonged and ultimately fatal illness, was the result of impairment of the pituitary-adrenal response to stress caused specifically by the lesion destroying the median eminence.

Neurosecretion

Although Gomori's chrome-alum-hematoxylin and phyloxine stain has been used extensively in the study of the neurosecretory systems of normal animals and man under a variety of experimental conditions,[3,11] its application to human pathologic material is still quite limited. To the authors' knowledge, this is the first time this particular technic has been applied to the study of human diabetes insipidus or allied hypothalamic disorders. The results were as might have been predicted on the basis of previous experimental work. For purposes of discussion, the paraventricular and supraoptic nuclei will be considered together; this is justified on the basis of the great morphologic similarity of their neurons and their blood supply, their common projection to the neurohypophysis, their mutual participation in neurosecretory phenomena, and their similar response to osmotic stimuli.[54]

Although the diabetes insipidus was well explained in case 1 by interruption of the supraopticohypophysial tract by the tumor nodule, the theory that the supraoptic neurons may do more than just innervate secretory elements in the posterior pituitary, but actually produce these hormones and transport them along their axons to the neural lobe[3] is of absorbing interest. Principal support for such a tenet comes from the selective staining properties of a granular material in the neurons, their axons, and the posterior lobe, and its behavior under certain experimental conditions. Evidence that the stainable material is the hormone or its carrier substance has already been cited.[4,5,7]

Thus one should expect in a case of clinical diabetes insipidus that this substance would be found missing or at least diminished. Such was the situation with case 1, in which no intact secretory neurons could be identified, and in which neurosecretory material was absent except for one tiny collection of granules in the posterior lobe. By the same token, some elements of the neurosecretory apparatus should be intact in the case of hypothalamic tumor without diabetes insipidus, although the proportion of intact units would not necessarily have to be high since from 85 to 90 per cent of the supraopticohypophysial system may be destroyed before the onset of diabetes insipidus.[14] In our second case, which showed no clinical disturbance of water metabolism, the hypothalamus was unrecognizable grossly and the pituitary stalk was greatly attenuated. The appearance of the pituitary on the Gomori stain was midway between that of the first case and the normal. Some areas showed condensation of pituicytes and absence of neurosecretion, while others retained the normal loculated appearance of the pos-

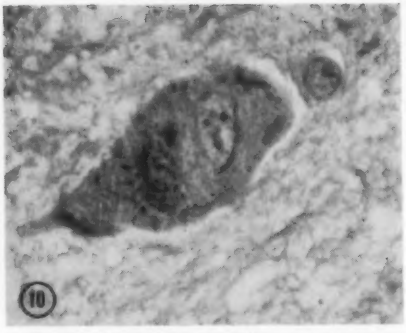


FIG. 10. Neuron from normal human supraoptic nucleus, containing abundant granules of neurosecretory material. Gomori stain.

terior pituitary and demonstrated well-preserved neurosecretory vesicles containing abundant granules. Unfortunately it was never possible to examine the proximal stalk, but examination of the nervous tissue at the lateral boundaries of the tumor showed intact granule-bearing neurons similar to those seen in normal supraoptic and paraventricular nuclei but probably belonging to the latter because of their position (figure 10). The proportion of neurons left intact could not be estimated, but their presence along with the presence of definite although reduced amounts of neurosecretory material correlates well with the absence of diabetes insipidus in this case. It would appear that the tumor had displaced the walls of the hypothalamus far laterally, but without destroying them and without completely severing the hypothalamus from the neurohypophysis. We believe these findings support the theory that the stainable neurosecretory material represents the active principle of the posterior lobe of the pituitary, in particular the antidiuretic hormone, and that the findings are consistent with the theory that it is produced by the above mentioned hypothalamic neurons. In addition, this staining technic has proved itself a valuable aid to the pathologic study of disorders affecting the secretory portion of the diencephalon.

Pathologic Considerations

We believe that the tumor in the second case was a fibrillary astrocytoma. A similar tumor characteristically in this same location has been described by Globus[55] and classified as an infundibuloma. From the clinical course as well as the histologic appearance, the growth rate of the tumor must have been slow, with increase by gradual expansion and compression of the neighboring structures rather than by invasion.

The primary tumor in case 1, showing diabetes insipidus and associated disturbances, was located in the posterior superior wall of the third ventricle, with secondary implants in the infundibulum and lamina terminalis but without direct involvement of the pituitary. It is, of course, possible that the tumor arose in the pineal body, but that structure was involved by the neoplasm only slightly. The bulk of the primary tumor contained mucus-bearing epithelium rather than the type of cells generally associated with pinealomas, and these epithelial tubules persisted in the thalamus after the mass had been greatly reduced in size following irradiation. Tumors arising in or near the pineal and spreading by implantation to meningeal or pial surfaces have been described previously, with diabetes insipidus from involvement of the tuberal region a not infrequent complication.[56–61] When the presenting symptoms have been due to a tumor in the chiasmal region without known involvement of the pineal but

showing a histologic picture similar to that of pineal tumors, the term "ectopic pinealoma" has been used.[62] Thorough study of autopsy specimens will usually reveal a primary in the pineal region in such cases, although this is not always so.[59,61] Conversely, it is altogether likely that cases reported in the literature of diabetes insipidus with pineal tumors but without apparent spread from the primary site in the roof of the third ventricle[13,63] were due to tuberal implants that were missed, for the present case demonstrates that serial sections may be required to find them. A case of diabetes insipidus following implantation of pineal tumor into the tuber cinereum was reported in 1936 by Stringer[16] and resembled ours in most respects, although the tumor implant was somewhat larger, being grossly visible, and no study was reported of the hypothalamus.

The primary tumor in our first case contained mucus-bearing epithelial tubules and loosely arranged tissue made up of primitive neuroglial cells. This would therefore seem to be a malignant teratoma with mature epithelial elements and a primitive, more rapidly growing embryonal tissue. Tumors with a very similar histologic structure have been described by Baggenstoss and Love[58] under the name of pineal ependymoma. The more malignant component of the tumor in the roof of the third ventricle, believed to be its neuroglial portion, was the source of the implants in the third ventricular floor. This component was quite radiosensitive as evidenced by its clinical response and by the histologic evidence of degenerative changes in the implants. The latter fact made identification of the constituent cell types in these locations much more difficult, but viable tumor cells resembling polar spongioblasts were seen abundantly in the advancing edge of the tumor nodules. Russell[59] believes that most pinealomas should be regarded as atypical teratomas. We have insufficient evidence to express an opinion on this point, but our case apparently falls into the group that she described. Tumors showing these features appear particularly prone to metastasize by secondary implantation.

SUMMARY AND CONCLUSIONS

1. Two cases of hypothalamic tumor are presented with the autopsy findings.

2. The material was examined with the routine histologic stains, and in addition the neurosecretory material was studied using the chrome-alum-hematoxylin and phloxine method of Gomori.

3. The first case, with diabetes insipidus and a very small tumor of the median eminence of the tuber cinereum, was associated with absence of neurosecretory material from the neurohypophysis and complete loss of the granule-bearing neurons of the supraoptic and paraventricular nuclei.

4. The second case, which had no evidence of diabetes insipidus but showed a large tumor apparently obliterating the hypothalamus, was associated with persistence of secretory neurons displaced far laterally by the tumor, and definite although reduced amounts of neurosecretory material in the neurohypophysis.

5. Because of the discretely localized nature of the lesion in case 1, an attempt is made to correlate symptomatology, in particular the disturbances in water and electrolyte metabolism and endocrine function, with the observable alterations

in hypothalamic and pituitary morphology.

ADDENDUM

Since this paper was submitted for publication, a report has appeared of a case of diabetes insipidus which at autopsy showed encephalomalacia of the upper pituitary stalk and absence of neurosecretory material in the hypothalamus and neurohypophysis (Drager, G. A. and Russell, G. V.: Observations on neurosecretion in the hypothalamo-hypophysial system in a case of diabetes insipidus in man [Abstract], Anat. Rec. 118:295, 1954).

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Constriction Pain in Muscle

Ischemic or Neural?

Michael Kelly, M.D.

IF MUSCLES ARE EXERCISED while their blood supply is arrested, they become painful.[1–3] The circulation of the arm is arrested by inflating a manometer cuff, and the forearm muscles are exercised by repeatedly clenching the fist. Pain and tenderness develop in the forearm muscles within 20 seconds and become intolerable within 40 seconds. When the circulation is released the pain vanishes within three seconds.

Lewis[3] concluded that a metabolite (factor P) was produced in the muscles and diffused out into tissues to act on pain nerve endings. Such a substance would have to remain stable during arrest of the blood flow; but it must be promptly washed away or neutralized when the circulation is restored.

After critical study, however, the author has begun to doubt, first, that ischemia of muscle is the primary cause, and second, that a humoral mechanism is the subsidiary cause of the pain.

If the pain were due to ischemia it should be hastened by anoxia,[4] but Harpuder and Stein[5] have clearly shown that the pain does not appear sooner in cyanosed patients. Furthermore, it is not hastened by vasoconstriction (reflex or pharmacologic) or delayed by vasodilatation.[5–7] Ischemic pain is not accelerated when the limb has been exsanguinated by an elastic rubber bandage, and it can develop in a limb whose circulation is not obliterated.

OBSERVATION 1.
PERSONAL EXPERIENCE OF ISCHEMIC PAIN

When the author's radial pulse had been obliterated by a manometer cuff with the mercury at 140 mm., pain developed after 20 contractions and became intolerable after 35. It was preceded by increasing fatigue, muscular weakness which progressed almost to paralysis, and increasing discomfort from the cuff which became intolerable. The four sensations merged, and fatigue, discomfort, and pain all became intolerable at the same moment.

Exsanguination by elastic rubber bandage. The author's arm and the arms of four other subjects were made bloodless; ischemic pain came on after 20 to 25 contractions in all. The same number of contractions was required in each case when the arm was constricted with a manometer cuff.

Nonocclusive constriction of the limb. With the mercury at 60 mm. and the pulse palpable, fatigue and pain came after 40 contractions instead of 20. The pain was less intense but of the same quality.

Comment. If the pain were due to ischemia, it should appear earlier when

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the arm is exsanguinated than when it is congested by a manometer cuff, and it should not appear when the circulation is not blocked.

DOES A METABOLITE DIFFUSE OUT OF THE MUSCLE FIBERS?

Lewis[3] was not completely satisfied with the idea of factor P as a humoral substance which diffused out of the fibers to the tissue spaces. It did not explain for him why the muscles took 20 minutes to recover from ischemic work. If they are put through the performance again in 10 minutes, pain develops after 12 contractions. Moreover, if they are fatigued from recent nonischemic work, ischemic pain develops sooner. Lewis believed that the changes inside the fibers induced secondary and distinct changes in the spaces, and it was only the changes outside the fibers which he called factor P, or the stimulus to pain.

The pain is not hastened by various changes in the intracellular pH,[8] nor by injections of lactic acid, histamine, or other supposed products of tissue metabolism.[5] All attempts to incriminate the known products of metabolism have failed. Factor P has qualities not possessed by any known chemical substance. Though it does not appear during 30 minutes of circulatory arrest, it appears rapidly and remains stable when the circulation is occluded and the muscles are working. Yet it is unstable, for it disappears in three seconds when the flow is restored.

How does it disappear? It must be either 1) neutralized or destroyed, or 2) washed away. 1) This implies that we all have in our blood a substance which neutralizes or destroys factor P, and that the amount in the forearm is completely used up by the quantity of factor P which is produced by a few ischemic contractions. Yet in the circulating blood there is sufficient of it to destroy within three seconds all the excess factor P which the contractions have produced. Chemical reactions on so gigantic a scale by two undetectable substances are completely incredible. 2) If factor P is washed away and not destroyed, we should expect it to affect the ischemic performances of other limbs. But Harpuder and Stein[5] generated ischemic pain in both legs and flooded the system with factor P by releasing both femoral cuffs simultaneously. Forty seconds later they began ischemic work in the forearm; the usual number of contractions was required to induce pain.

What other substances do we know which cause pain in muscles? Are any of them so diffusible that they can be washed away in three seconds? Two examples come to mind: 1) When hypertonic saline is injected into muscle, pain reaches its maximum in five seconds and takes more than 30 seconds to disappear.[3] 2) When a 1 per cent solution of potassium chloride is injected intra-arterially into a muscle, pain rises to a maximum in 30 seconds and persists for 10 to 45 minutes.[5] It is unlikely that any unknown chemical substance is more diffusible than sodium chloride or potassium chloride, or that it can be washed away completely in three seconds.

EFFECT OF HEAT

Pain can be produced without any muscular effort when the ischemic arm is put in hot water for five minutes.[5] After a shorter heat stimulus, the pain is brought on by only a few muscular contractions. Cold water, on the other hand, delays the onset of pain until more than the usual amount of work has been done. Ischemic pain can be produced in

nonmuscular tissues if they are warmed; when a finger is ligated and immersed in hot water it stings in one minute.[5]

Heat can do what neither vasodilatation nor vasoconstriction can do – accelerate the onset of pain. It has been suggested that it accelerates cellular metabolism, but this cannot be the cause of the cutaneous pain. Heat lowers cutaneous pain thresholds by rendering receptors more sensitive.[3] When non-painful sunburned skin is put in warm water, it develops a burning pain, and when painful sunburned skin is put in cold water it ceases to burn.

DAMAGE TO NERVES

We should not forget that nerves as well as vessels are damaged when the limb is constricted.[6,9–13] There is an increased discharge both from the compressed nerve[9] and from its peripheral field.[13] Deep reflexes are abolished in muscles performing ischemic work, and muscular coordination is so poor that the patient's signature is unrecognizable.[14]

Nathan[13] has shown that the nervous discharge from painless lesions of skin and muscle is increased during ischemia. When the limb has been constricted, a painless blister on the skin begins to burn and a painless area of damage to muscle aches. Compression of the nerves of the arm, without occlusion of the circulation, was sufficient to generate pain from the previously painless muscular and cutaneous lesions. Though these effects have been attributed to ischemia of nerves, they are more likely to be due to direct damage.

OBSERVATION 2. CIRCULATION OCCLUDED WITHOUT PRESSURE ON NERVES

Brachial artery occluded by finger. In three subjects with the artery digitally compressed just firmly enough to abolish the pulse, the median nerve was not compressed. Though the whole forearm and hand became extremely pale, 60 contractions were required to bring on pain (with manometer cuff the number was 25). In the author and two others, however, pressure on the median nerve could not be avoided and the pain appeared at the usual time.

Subclavian artery occluded by finger. In a boy aged 16 the pulse was abolished by digital compression of the subclavian artery. Though his hand became pale, he could perform 100 contractions painlessly.

OBSERVATION 3. NERVES PARTIALLY BLOCKED WITHOUT OCCLUSION OF CIRCULATION

When the knees are crossed, the lateral popliteal nerve can be rolled between fibular head and patella. It was firmly compressed until the outer side of the foot tingled. Then the calf muscles and the anterior tibial group were contracted alternately. Soon an intolerable ache began in the anterior tibial group and radiated to the foot. There was no aching in the calf muscles, whose nerve supply was not compressed. The pain disappeared as soon as the pressure was released, though the movements continued.

When the ulnar nerve is compressed at the medial epicondyle and the fingers clenched several times, aching and fatigue develop in the hand.

When the ulnar nerve is partially blocked with 0.5 per cent Procaine solution, painful fatigue develops in the hand and the ulnar side of the forearm after a very few muscular contractions.

In nerve injuries it is commonly observed that partially innervated muscles are prone to fatigue and to painful cramps. They have to be carefully protected from excessive work.

DISCUSSION

If the pain were related to the blood supply its onset would be delayed by vasodilatation and accelerated by anoxia, vasoconstriction, and exsanguination. As we have seen, the pain develops in fatigued muscles with a free blood supply whose nerve supply is partially blocked, and it does not develop readily if the nerves are left free though the circulation is occluded. Clearly the pain is not due to ischemia.

Fatigue develops in the muscles, then pain. Fatigue is a definite muscular sensation which, when intensified, progresses to aching pain. For example, while dissecting a cadaver, the author wore tight rubber gloves which hindered finger movements. Weakness of the fingers developed and progressed almost to paralysis, and fatigue in the forearms progressed to an intolerable ache resembling ischemic pain exactly.

When a limb is constricted it becomes generally hyperalgesic, skin becomes hyperesthetic,[12] and deep wounds become more painful.[15] Heat summates with hyperalgesia – due either to a blister[3] or to constriction[5] – to give a stinging cutaneous pain. Similarly, hyperalgesic spots in muscle become painful by summation when its nerve is compressed.[13] If for a hyperalgesic spot we substitute a working muscle, subthreshold is again raised to threshold by compression of the nerve. Muscular fatigue is therefore a subthreshold condition analogous to hyperalgesia; it becomes pain when it is intensified by partially blocking the nerve supply.

SUMMARY

1. So-called "ischemic" pain in muscles is not due to ischemia but to pressure on nerves.

2. The pain is not intensified by anoxia or by reducing the blood supply to the muscle, nor reduced by increasing the blood supply.

3. No product of metabolism possesses the qualities required by factor P.

4. Ischemic muscles can be exercised painlessly when their nerve supply is not compressed.

5. Fatigue and pain develop during exercise when the nerves are partially blocked without circulatory occlusion.

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Epidemiologic Investigations of Amyotrophic Lateral Sclerosis

2. Familial Aggregations Indicative of Dominant Inheritance

Part I.

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NUMEROUS HYPOTHESES of the etiology of amyotrophic lateral sclerosis have been suggested since Charcot described the disorder more than 75 years ago, but the etiology and the pathogenesis remain unknown. It has often been reported that the classic form of the disease is nonfamilial and nonhereditary,[1–6] although reports of familial occurrence have been forthcoming at intervals since 1850. In this paper the familial incidence of amyotrophic lateral sclerosis will be reviewed in detail, with a description of those cases found in the literature and of several additional pedigrees and other data which we have obtained. References to familial aggregations of amyotrophic lateral sclerosis are widely scattered in the literature, and no recent attempt has been made to our knowledge to collect and classify such material clinically. We shall also attempt to analyze by statistical means some of the genetic characteristics of the collected pedigrees.

These studies were initiated by the reports of the high incidence of a classic form of amyotrophic lateral sclerosis on Guam by Arnold and associates[7] and by Koerner[8] and our subsequent experience in the Mariana and the Caroline Islands. The prevalence rate for amyotrophic lateral sclerosis on Guam and Rota is about 420 per 100,000 population as compared to about four per 100,000 population for various North American and European countries. No external etiologic agent has yet been detected to explain this high prevalence, but a marked familial aggregation of cases has been noted.[8,9] Although familial aggregation of cases might be due to a common environmental factor as well as to a genetic influence, the distribution of cases among the various peoples in the area is more suggestive of a genetic influence than of an environmental factor.[9]

Koerner reported a "positive family history" in 40 per cent of the cases that he observed on Guam, and in our pre-

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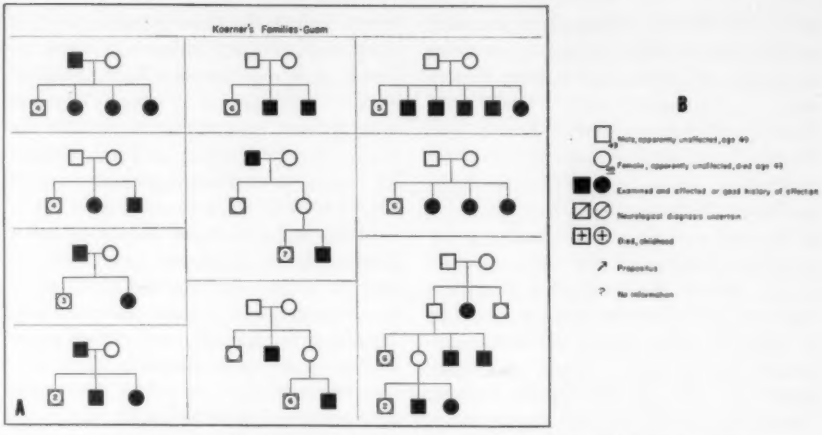


FIG. 1. *A.* Pedigrees of selected families in which amyotrophic lateral sclerosis occurred on Guam, after Koerner (1952).[8] *B.* Code for pedigrees in figures 1A through 14.

liminary studies we observed a similar familial aggregation of cases where the "family" was limited to offspring, parents, grandparents, aunts, uncles, and first cousins.

Figure 1A illustrates the pedigrees which Koerner[8] had noted among some Guamanian families in which amyotrophic lateral sclerosis occurred. Although these pedigrees are now known to be incomplete, they demonstrate that ancestors as well as siblings are affected. We are refining and extending this investigation of pedigrees on Guam, and our recent data give the impression that familial aggregation of cases is the rule and not the exception there. For example, in one family in a southern village of Guam we have obtained a recent history of amyotrophic lateral sclerosis in three siblings, a paternal uncle and aunt, and four paternal cousins, and we have found that in this particular family amyotrophic lateral sclerosis has been highly prevalent for generations. Although numerous instances of multiple cases of typical amyotrophic lateral sclerosis in the same family were noted, we found no arrested form, as described by Swank and Putnam,[10] nor any rudimentary form, as described by Dawidenkow.[11,12]

Figure 1B shows the code for pedigrees in figures 1A through 14.

The details of the Guam genetic and epidemiologic studies will be presented at a later date. Since the Guam findings suggested a hereditary rather than an external causative factor, we decided to reevaluate thoroughly the possible genetic factors in classic amyotrophic lateral sclerosis. The principal purpose of this report is to present a thorough, although not necessarily exhaustive, review of the literature and to include several additional pedigrees as evidence that amyotrophic lateral sclerosis may occur as a hereditary disease.

THE CLINICAL SYNDROME: PROBLEMS OF DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION

Amyotrophic lateral sclerosis as referred to here is the primary or classic

form of unknown origin. It is a motor system disease characterized by anterior horn cell and corticospinal tract degeneration. We agree with Grinker and Bucy,[2] with Adams, Denny-Brown, and Pearson,[6] and with Robertson[13] that the progressive muscular atrophy of Aran-Duchenne, amyotrophic lateral sclerosis of Charcot, and progressive bulbar palsy are all variations of the same disease. It is a disease of middle life, with two thirds of the cases developing between 35 and 55 years of age. It rarely occurs before the third decade and infrequently as late as the eighth decade. The onset is insidious, and the course is progressive with death inevitable, usually in about three years, infrequently in less than one or as long as ten years. The characteristic clinical signs and symptoms are progressive weakness and atrophy with fasciculation and fibrillation of the affected muscles. Most commonly these begin in the small muscles of one hand although they may begin in any of the striated musculature. Usually the corticospinal tracts become involved at some time in the course of the disease, giving rise to spasticity in the extremities. Frequently, the spasticity in the lower extremities contrasts with atrophy and flaccid paralysis of the upper extremities. Associated with the corticospinal tract involvement there may be pseudobulbar symptoms, hyperactive reflexes, and Babinski signs.

If the involvement of the corticospinal tract comes late in the course of the disease, the signs of this involvement may be completely masked by the extensive muscular atrophy and the disease is then referred to as "progressive muscular atrophy." Similarly, if the disease begins in the bulbar musculature, death may occur early because of aspiration pneumonia before the development of other symptoms and the disease is then referred to as "progressive bulbar palsy." Sensory and mental symptoms are seldom present, and in our experience the ocular muscles are not involved; similarly, vesical incontinence and absence of superficial reflexes are rarely seen.

Additional variants of the amyotrophic lateral sclerosis syndrome have been described. These we have not included in the amyotrophic lateral sclerosis syndrome, since clinically and pathologically they seem quite distinct. Such variants include the so-called "juvenile" amyotrophic lateral sclerosis, and very slowly progressive muscular atrophy with involvement of the external eye muscles. Gilsanz[14] has carefully reviewed the numerous reports of juvenile and childhood amyotrophic lateral sclerosis and progressive muscular atrophy, most of which were originally designated by the authors as "familial spastic paralysis associated with amyotrophy." These are most frequently reported in siblings only, and this fact is suggestive of a recessive inheritance although a few cases with a dominant genetic pattern have been reported.[11,15–17] The disease begins at an early age and tends to run a very slow, progressive course with the duration often measured in decades.[10,11,18–20] No report has come to our attention of the simultaneous occurrence in the same family of classic amyotrophic lateral sclerosis and "juvenile" amyotrophic lateral sclerosis. In one instance in which we noted familial spinal paralysis with slight amyotrophy in a family on Guam, there was no apparent relationship between the members of the family and the numerous families on the island in whom the typical adult form of amyotrophic lateral sclerosis did oc-

cur.[21] In the opinion of others[13,14,22–24] as well as ourselves and Iriarte,[21] these cases of "juvenile amyotrophic lateral sclerosis" are more closely related to the hereditary ataxias than to classic amyotrophic lateral sclerosis.

In rare instances a form of muscle atrophy has been reported in which progression occurs over a decade or more and in which corticospinal tract involvement is absent or minimal.[10] In two extensive pedigrees reported by Myrianthopoulos,[25] in whose report there is incidentally an extensive review of the literature on progressive external ophthalmoplegia, such a slow, progressive atrophy with external ophthalmoplegia as the important component is described. Many of his patients had only involvement of external eye muscles; in others, the muscle atrophy was often typical with a very slow, progressive course, in which a duration of ten years or longer was frequently noted, and with the presence, only occasionally, of lateral column involvement. The clinical disorder described in these families is not similar to the cases of amyotrophic lateral sclerosis that we have seen, and we do not consider these as part of the amyotrophic lateral sclerosis symptom complex.

EVIDENCE AGAINST THE HEREDITARY ORIGIN OF AMYOTROPHIC LATERAL SCLEROSIS

The general impression regarding heredity and amyotrophic lateral sclerosis is well summarized by Dawidenkow[11,12] as follows: "It has been understood since Charcot's time that direct or indirect heredity plays no part [in the etiology] of amyotrophic lateral sclerosis." Wilson[1] stated that "direct inheritance [in amyotrophic lateral sclerosis or progressive muscular atrophy] is extremely rare," and Adams, Denny-Brown, and Pearson[6] as recently as 1953 stated that "it is not familial."

In 1944, Wechsler and associates,[5] in reviewing the case reports of 81 patients seen at Mt. Sinai Hospital in New York City, stated: "There was no history of familial incidence of amyotrophic lateral sclerosis in any of the cases, so that hereditary factors can be excluded." In 1949 Van Bogaert[26] reported, "The familial form is exceptional in this disease [amyotrophic lateral sclerosis]. In the present state of our research, we have 67 clinico-anatomic observations and have not seen a single familial or hereditary form in the adult." In his discussion of progressive muscular atrophy he stated, "We know only of a few old case histories of the type of Aran-Duchenne that were considered as being familial. We have no recent observations that are convincing."* In 1952 Müller[27] reviewed 190 cases (98 cases of amyotrophic lateral sclerosis, 22 cases of progressive bulbar palsy, 44 cases of progressive spinal muscular atrophy, and 26 cases with progressive bulbar and spinal muscular atrophy) and reported, "No hereditary factor was found."

Dawidenkow[11] developed extensive pedigrees on 12 patients who had amyotrophic lateral sclerosis and examined 28 relatives of the 12 patients. He was unable to discern any amyotrophic lateral sclerosis among these or other relatives. He reported hypoactive muscle-stretch reflexes in about half of the 28

*In a recent paper, van Bogaert and Radermecker (Monatschr. f. Psychiat. u. Neurol. 127:185-203, 1954) reported two cases of hereditary amyotrophic lateral sclerosis, one of them verified at necropsy. Because our paper was finished before the report by van Bogaert and Radermacher was available, this family is not included in the tabulations in part 2 of our report.

family members examined, which he concluded was indicative of a rudimentary form of the disease.

Curtius and Pass[28] selected seven patients on whom clinical and necropsy findings were those of amyotrophic lateral sclerosis but failed to learn of any other case among 253 blood relatives of these patients. They stated, "This corresponds to the same negative findings of Dawidenkow and numerous other literary references on the subject; namely, that only very rarely does the affliction show multiple occurrence in a family." They reported that no rudimentary form of the disease could be detected in any of these family members. Although the results of their own investigations were negative, they indicated that their group was small and that even for neurologic diseases in which a genetic factor is generally considered to be present, such as syringomyelia and subacute combined degeneration, only a small percentage of the pedigrees appear to have multiple cases in the family.

EQUIVOCAL EXAMPLES OF FAMILIAL AGGREGATIONS OF AMYOTROPHIC LATERAL SCLEROSIS

Before proceeding with a description of the cases and of the pedigrees of familial amyotrophic lateral sclerosis which we find acceptable, we shall first briefly review several reports which have been widely quoted in the literature as familial cases of amyotrophic lateral sclerosis but which, we believe, are either variants of the amyotrophic lateral sclerosis syndrome or conditions which have been misdiagnosed as amyotrophic lateral sclerosis or progressive muscular atrophy.

According to Grinker and Bucy,[2] Moleen, in his paper entitled "Familial Progressive Mucular Atrophy," described an illness in three brothers "who were afflicted in identical manner." On examining Moleen's paper,[29] it was our opinion that the cases described were not progressive muscular atrophy but typical cases of myotonia dystrophica.

Paulian and Cardas[30] described the occurrence of amyotrophy of Aran-Duchenne type in the left upper extremity of two sisters. One sister noted the insidious onset of weakness, atrophy, and muscle fasciculations at age 23 years, and the other at age 22 years. On examination the first showed some atrophy in the left hand, slight muscle atrophy with fasciculations in the left arm, hyperactive brachioradial reflex in the same arm, and a "neutral" left plantar response, whereas there was a "flexor" response on the right.

The younger sister noted weakness in her left hand one month after the older sister had had her first symptoms. The left hand was said to be weak, and there was slight atrophy in the first interosseous space. The deep reflexes were brisk in the left arm; there was no Babinski sign.

Unfortunately, no follow-up on these patients nor any additional family history is reported. Although these cases are referred to as "amyotrophic lateral sclerosis: monoplegic and familial types," it is difficult, with the information available, to accept these cases as classic amyotrophic lateral sclerosis.

Gates,[31] in his textbook *Human Genetics*, stated that "Bremer (1922) described a family [having amyotrophic lateral sclerosis] with 11 cases (9 male, 2 female) in two generations, sibships 11 affected: 12 normal, inheritance dominant with no skip." Bremer,[17] however, reported that this family had "a spastic form of heredodegeneration of the nervous system, which is clinically *allied to* amyotrophic lateral sclerosis." Two of the 11 patients were examined by Bremer: "In one, stiffness of gait and atrophy of the calves were noted at age 22 years. At age 26 years the hand strength decreased and his hand muscles became atrophic and a scanning type of speech developed. On examination the patient had a steppage gait with a broad base stance. There was a suggestion of facial grimacing and forced laugh-

ter. There was no nystagmus, strabismus, or intention tremor. Both optic disks showed temporal pallor. There was muscle atrophy in both upper and lower extremities which increased distally. . . . The patient was still living at age 38 years."

The sibling of the foregoing patient had a similar history and physical findings, including temporal pallor of the optic disks, except for the following: onset in his case was noted at age 14 years, muscle stretch reflexes were hyperactive, Babinski sign was present bilaterally, and the feet were kept in the equinovarus position. This patient was still living at age 31 years.

The disease as described in the other members of the family had its onset in adolescence in several members of the family; the age at onset in several of the others is uncertain. In some of these cases, mental deficiency and ataxia are described.

Rütenik,[32] in a paper entitled "Familiäre amyotrophische Lateralsklerose," published in 1937, described the occurrence of a very slowly progressive neurologic disorder in two mentally deficient sisters. One sister was observed by Rütenik, and her case is described in detail: Progressive spasticity of gait, sensory disturbances, and vesical dysfunction were first noted about 17 years of age. About ten years later, there was slurring of speech and amyotrophy "without weakness" in one hand. She died of pneumonia at age 45 years, 28 years after onset of neurologic symptoms. The postmortem examination showed some general atrophy of the brain, degeneration of the substantia nigra, marked demyelination of the pyramidal tracts, and moderate demyelination in spinocerebellar tracts and the lower two thirds of the posterior column. There was marked degeneration of the ganglion cells in the gray matter of the spinal cord, particularly in the anterior and lateral horns but also in the column of Clarke. Degeneration was fairly widespread in some layers of the cerebral cortex aside from the motor cortex, and degeneration was noted in sensory as well as motor nuclei in the brain stem.

This patient's sister died at age 38 years of a similar affliction after 21 years' duration, and a brother, who was examined in late adult life, was found to have bilateral Babinski signs in the absence of any other neurologic signs or of any complaints.

These reports are reviewed in some detail to indicate the syndrome which has been referred to by some authors as a hereditary form of amyotrophic lateral sclerosis but which does not conform to the definition that we and others have accepted for amyotrophic lateral sclerosis.

REPORTED FAMILIAL AGGREGATIONS OF AMYOTROPHIC LATERAL SCLEROSIS

In many of the textbooks of neurology of the late nineteenth century, progressive muscular atrophy of adults is described as a hereditary disease. However, over the past 50 years thinking on this subject has changed so that today, in almost every recent clinical report and modern textbook of neurology, classic amyotrophic lateral sclerosis and progressive muscular atrophy are said to be nonfamilial and nonhereditary. This widespread impression, we believe, is erroneous for, as we shall show, there are numerous accurate pedigrees of classic progressive muscular atrophy and amyotrophic lateral sclerosis scattered throughout the medical literature, and we have found that additional instances of familial aggregation of cases are not uncommon.

The earliest report which we could locate was that of the case history which Aran[33] included in his description of progressive muscular atrophy published in 1850. In this he described the progressive muscular atrophy in a 45 year old sea captain and stated that one sister and two of the mother's brothers had also died of a general muscular atrophy. Three brothers and two sisters of the patient (ages not given) were still living and had not been affected. The patient noted an insidious onset of cramps and muscle quiverings in his forearms which were followed by weakness and atrophy. Later there was similar involvement in the lower extremities. Opposition of the thumbs was the most extensive loss in the upper extremities at first. There was considerable

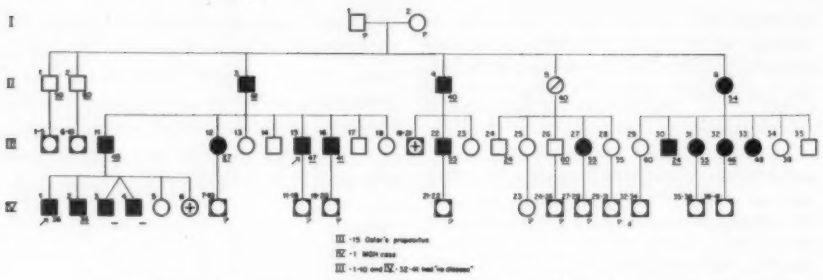


FIG. 2. Pedigree of Vermont family in which progressive muscular atrophy occurred, after Osler[34] and Brown.[35]

muscle atrophy in both upper extremities and in the lower extremities, particularly on the right side. Respiratory movements became more difficult and the patient died two years after he had noted his first symptoms.

In 1880, Osler[34] described progressive muscular atrophy in 13 adults in two generations in the Farr family of Vermont.

The propositus (III-15 in figure 2), Erastus Farr, a 47 year old farmer, developed painless weakness and wasting with muscular twitchings in the left thigh and buttock. When Osler examined him about one year after onset, he had severe weakness and atrophy in the left lower extremity, and muscle "fibrillary twitchings" were noted in all four extremities. Of the 12 other affected members of this family, ten had already died of progressive muscular atrophy and two had early symptoms.

Dr. Madelaine Brown recently enlarged the genealogy of the same family with a 1905 Massachusetts General Hospital case report[35] of progressive muscular atrophy in a member of the same family which Osler had described in 1880. The pedigree (figure 2) is based on the reports by Osler[34] and by Brown,[35] supplemented by the additional family history and other information, including Osler's collected letters which Dr. Brown had examined.

The patient, who was seen at the Massachusetts General Hospital, was a 35 year old artisan (IV-1) who had noticed progressive weakness in the skeletal musculature beginning in the right thigh. "Fibrillary twitchings were present in both thighs. Sensation was intact. Deep reflexes in the arms were intact. The right knee jerk was sluggish, the left lively. There was no clonus, and normal plantar responses were obtained. The abdominal and cremasteric reflexes were present . . . ."

"It has recently been ascertained that all three brothers (IV-2, IV-3, and IV-4) of the patient admitted to the Massachusetts General Hospital died of progressive muscular atrophy. One sister (IV-5) did not have the disease."[35]

Unfortunately, no postmortem studies have been reported in members of this extensive pedigree.

Hammond,[36] in the section on "Progressive Muscular Atrophy" in the 1881 edition of his *Treatise on the Diseases of the Nervous System*, reported that "hereditary influence of most cases would be considered as acceptable. Of 46 cases, there were two sets of brothers, and 14 others had relatives affected with the disease. . . .

"By far the most remarkable history of the hereditary transmission of the disease, which has come to my personal knowledge, is contained in the following account, which constitutes a pamphlet written by one of the unfortunate subjects, and sent by Dr. R. F. Andrews of Gardner, Masachusetts . . . ."

He then quoted, in full, the story of

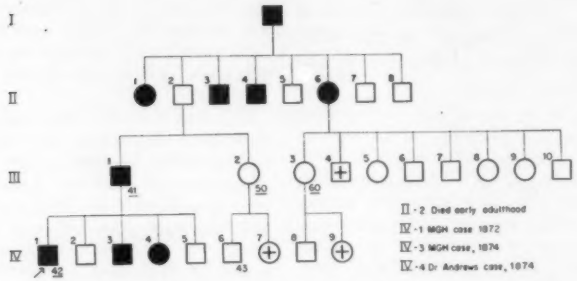


FIG. 3. Pedigree of Massachusetts family with progressive muscular atrophy, after Hammond[36] and Brown,[35] and modified by Myrianthopoulos.[25]

"Muscular Atrophy," which is referred to as the "Wetherbee Ail," by the patient who described his own illness and that of his father, four siblings of his grandfather, and his great-grandfather. The pedigree illustrated in figure 3 is based on Myrianthopoulos's modification[25] of the one presented in Dr. Madelaine R. Brown's article on the "Wetherbee Ail." [35] "The persons were native-born Americans. Mrs. Spaulding [III-3, an elderly cousin] thinks we descended from the English . . . . There are branches of the family in which nothing of the kind appears; there is nothing of it in the Wetherbees in Scotland. Mrs. Spaulding thinks the disease was in the family previous to the time of my great-grandfather." [36]

The patient described the affliction in his father (III-1), who, at the age of 39 years, "discovered a weakness in the right thumb . . . The larger muscles of the arms and legs became soft and flabby, and diminished in size." The condition progressed and he died of respiratory embarrassment and renal complications about 26 months after onset of symptoms.

The propositus himself (IV-1) noted some "fibrillous contractions" in the right thigh in 1870 (at the age of 39 years) but these disappeared in a few days, and it was not until about a year later that he noticed progressive muscle weakness and wasting in the same area. Progressive weakness and atrophy with muscle twitchings developed in all four extremities. The progress was especially rapid "in the ball of the right thumb and the left thigh." There were no remissions and no loss of sensation. The patient completed the writing of the document on his illness on March 31, 1873.

Hammond then reported that he had received a letter the following year from the physician, in Gardner, Massachuetts, who stated that the patient had died in December 1873, and that the patient's sister (IV-4) "recently consulted me with symptoms of the same disease. The left arm and shoulder are affected. The twitching of the fibrillae is worse at night."

The remarkable document of the "Wetherbee Ail" was recently rediscovered by Dr. Madelaine R. Brown who, in addition, found that one of the patient's brothers (IV-3) became afflicted and was examined at the Massachusetts General Hospital in 1874 shortly after the propositus had died. Although some of the clinical details are lacking in these histories, the descriptions which are presented leave little doubt that progressive muscular atrophy, often with bulbar palsy but without ophthalmoplegia, was the affliction in this family.

Gowers,[37] in the chapter "Chronic Spinal Muscular Atrophy" of the 1888 edition of his *Manual of Diseases of the Nervous System*, stated:

Heredity is to be traced only in less than half the cases, and generally as an indirect neuropathic disposition. Rarely there is direct inheritance of the disease. Among instances that I have met with are a lady whose mother died from a similar atrophy, and another case (with illustrations of sections of the spinal cord) in which a brother had died from some chronic disease of the cord, attended with wasting.

Bernhardt[38] published an article in 1889, entitled "Ueber eine hereditäre Form der progressiven spinalen mit Bulbärparalyse complicierten Muskelatrophie." He did not refer to the cases as Charcot's amyotrophic lateral sclerosis. However, the clinical description leaves little doubt but that progressive muscular atrophy, with bulbar involvement as part of amyotrophic lateral sclerosis, was present (figure 4).

Several descendants (II-1, III-6, III-9) of a brother and sister (generation I) developed progressive painless paralysis with muscle atrophy and some fasciculations involving the neck, shoulder, arms, tongue, and face. There were progressive dysarthria and dysphagia; there was no ataxia, tremor, sensory disturbance, or mental disturbance. In II-1, the knee jerks were markedly increased. (The Babinski sign had not yet been described.) The illness was steadily progressive and of two to two and one-half years' duration in these three patients who died at ages 41, 33, and 37 years, respectively.

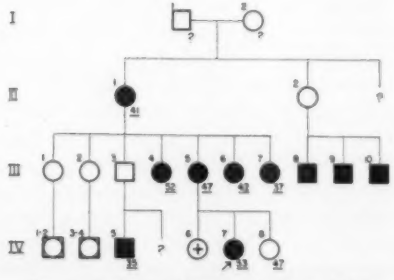


FIG. 4. Pedigree of German family in which progressive muscular atrophy and progressive bulbar palsy occurred, after Bernhardt.[38]

The father of II-1 was said to have had some brain disturbance, the nature of which was uncertain; he died at age 50 years. No information is available regarding his sister (the grandmother of III-6 and III-9). II-3 had died many years before at about 55 years of age of a "spinal cord disease." II-4, the mother of III-9, died at about 50 years of age of bulbar palsy and progressive muscular atrophy involving the neck, shoulders, and upper extremities. No pathologic studies were made, and no information was available on siblings or parents of the brothers and sisters in generation I.

Bruining[39] in 1904 described a progressive muscular wasting disease in a German father and son but referred to the condition as "chronic anterior poliomyelitis."

At age 45 years the father developed a progressive paresis and muscle atrophy with "muscle fibrillations" beginning in the right thigh. Within six months the upper extremities were also involved. The disease progressed without fever or remissions, and the muscle weakness seemed to spread distally in the extremities. There were no sensory disturbances. Later, difficulty in breathing and speaking occurred; 18 months after onset the patient died of bronchitis and pneumonia. The postmortem examination of the nervous system was limited to the spinal cord, where there was marked diminution in the number of anterior horn cells and slight demyelination in the pyramidal tracts. No signs of inflammation were noted.

The son, aged 23 years, the oldest of 13 children, developed progressive weakness and muscle atrophy in the neck and shoulder muscles. Within nine months there was almost complete paralysis of the muscles of both arms, the thorax, and especially the intrinsic hand muscles as well. There were no sensory changes; bladder and bowel functions were intact; muscle-stretch reflexes in the upper extremities were absent. After 15 months the patient succumbed to an intercurrent pulmonary infection. There was no necropsy.

No additional family history was given.

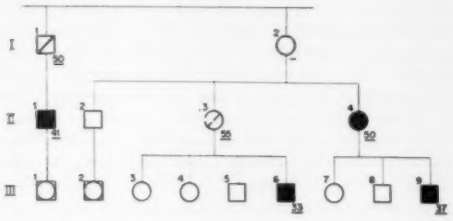


FIG. 5. Pedigree of New York family in which progressive muscular atrophy occurred, after Dana.[40]

Dana[40] in 1914 reported a family of "old American stock, coming from the state of New York," which had what he referred to as "chronic anterior poliomyelitis, beginning after middle life." "I venture to report here a case of this kind occurring at the age of 53, in a family in which ten cases were known to have developed in three generations . . . .

"I have no data by which to prove definitely that the lesion is an anterior poliomyelitis, and it may well be that it is not strictly inflammatory but rather a degenerative process."

Figure 5 shows the pedigree of this family.

The propositus, a 53 year old nurse (IV-7), was seen in April 1913, with the history of progressive weakness and atrophy of the left thigh, beginning in the previous January. Aside from absent left knee jerk and both ankle jerks, the reflexes were normal. Cranial nerves, sensation, and the results of laboratory tests, including Wassermann, were normal. Two months later there was weakness of the right thigh and of the fingers of the left hand. "Muscle flickerings," which were rather annoying and which also "had bothered her mother a great deal," were noted. The patient became progressively worse and died, presumably of bulbar involvement, ten months after onset of the disease. The duration for others in the family was believed to be about a year.

The propositus (designated by an arrow) had an older sister who died in infancy and a younger sister who died of "a gastric ulcer." Their mother (III-5) "died of progressive paralysis at the age of 47. In her case the disease began in the fingers and then went to the legs and throat and the whole trouble lasted a year. . . . The mother had three sisters who died of the same trouble, one at age 52, one at 42, and one at 37. In two of these cases the trouble began in the arms, and in one case in the legs. In all cases the disease progressed upwards."

The mother had an older brother (III-3) who was well but "whose son (IV-5) developed the trouble at age 35." Two other sisters remained well, as did all their children, some of whom were more than 50 years of age at the time of the report. The "maternal grandmother (II-1) had the same disease and died of it in her forty-first year. Maternal grandfather (not shown in figure) was healthy. . . . . Three sons of the grandmother's sister (II-2, she was not affected) died of the family disease."

Robinson[41] in 1917 described progressive muscular atrophy in a 36 year old man and three of his relatives.

Painless weakness and wasting were first noted in the right hand. There was progressive weakness and wasting with muscle twitchings in both upper extremities. No cerebellar or sensory symptoms were noted and the patient died of respiratory paralysis 18 months

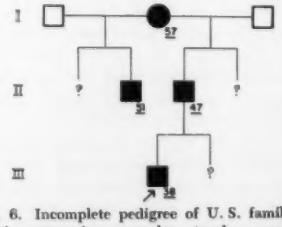


FIG. 6. Incomplete pedigree of U. S. family in which progressive muscular atrophy occurred, after Robinson.[41]

after onset of symptoms. The available genetic data are illustrated in figure 6. Unfortunately, no further information on the family was included. The patient's father died of progressive muscular atrophy at age 47 years after an illness of 18 months, and the patient's paternal grandmother died at age 57 years of the same disorder after one year. Of special interest is the fact that the patient's father had a half brother (same mother) who also died of progressive muscular atrophy at age 51 years after one year of illness.

In this pedigree there are four affected members in three generations; all four noted their first symptoms of weakness and wasting in the right upper extremity.

Hamilton[42] in 1918 presented data on four cases of familial progressive muscular atrophy in three generations (figure 7).

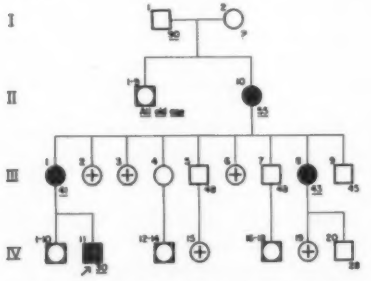


FIG. 7. Wisconsin family in which progressive muscular atrophy occurred, after Hamilton.[42]

The propositus, aged 30 years, was a railroad fireman from Wisconsin who first developed muscle aching in the upper and lower extremities and weakness, followed by atrophy, in the anterior aspect of the left thigh. Gradually weakness and atrophy with "muscle fibrillations" developed in the left tibial muscles, the muscles of the left hand and arm, the face, the tongue, and the right upper extremity. There was no sensory disturbance.

A few weeks before the patient died, there was marked muscle atrophy and weakness in the left extremities and moderate atrophy and weakness in the upper right extremity, the face, and tongue. Respiration and swallowing were difficult. At this time he was found to have nystagmus on right lateral gaze but not on gaze to the left or upward. Respiration became progressively difficult and the patient died one year after onset of symptoms.

At necropsy, the brain and viscera, aside from the pancreas which had an old hemorrhage, were grossly normal. Histologic examination of significance was limited to the skeletal muscles and central nervous system. There was irregular degeneration of muscle fibers interspersed with bundles of normal fibers. In areas where degenerating fibers were present, the number of nuclei about the degenerating fibers was greatly increased. The picture as described is compatible with chronic muscle atrophy. Examination of the spinal cord revealed a diminution of ganglion cells, particularly on the left side, in the anterior and lateral horns, and also somewhat in Clarke's column. There was a high degree of degeneration in the remaining cells of the anterior and lateral horns. Demyelination was present in the lateral and anterior columns, particularly the crossed and direct pyramidal tracts.

Montanaro and Lopez[43] in 1931 described a pedigree of an Argentinian family in which amyotrophic lateral sclerosis is said to have occurred in the father and three of his four offspring (figure 8). No amyotrophic lateral sclerosis was present on the mother's side, although many of her relatives were said to be "neurotic."

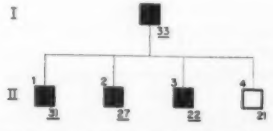


FIG. 8. Pedigree of Argentinian family in which amyotrophic lateral sclerosis occurred, after Montanaro and Lopez.[43]

The father (I-1) was of Spanish descent and had died 20 years before with "Charcot's disease with bulbar onset," at the age of 33 years. The oldest son (II-1) developed bulbar palsy following the flu. This was followed by progressive muscular atrophy in the upper extremities with hyperactive reflexes in the lower extremities. The Babinski sign was absent and

cerebrospinal fluid was said to be normal. Death occurred after two and one-half years of illness. The second son (II-2) developed muscle atrophy in the right arm and later in the left arm. He died of respiratory embarrassment two years after onset of symptoms. The third son (II-3) was said to have died at age 22 years after an illness of three years characterized by progressive muscular atrophy in the upper extremities and, later, a "bulbar syndrome."

Lovell[44] in 1932 described the occurrence of progressive bulbar palsy in a 66 year old Michigan woman. The history revealed that the patient's mother, a maternal uncle, and the uncle's son had each died from the same cause. The pedigree (figure 9) would be compatible with a dominant inheritance.

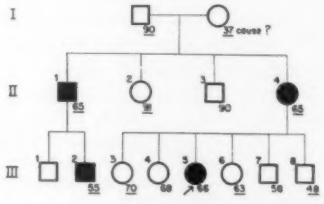


FIG. 9. Pedigree of U. S. family in which progressive muscular atrophy and progressive bulbar palsy occurred, after Lovell.[44]

Dittel[45] in 1940 described the occurrence of amyotrophic lateral sclerosis in eight patients in three generations, as illustrated in figure 10.

The propositus, a mentally alert person, developed dysarthria and dysphagia at the age of 52 years. Within eight months there was weakness in the left arm and hand, with obvious atrophy in the first interosseous space. On examination several months later weakness and wasting of the tongue and face muscles with muscle twitchings were noted. There were paresis of the palate and larynx and atrophy in the left hand. The left triceps reflex was hyperactive, the remaining reflexes being normal. The cerebrospinal fluid was essentially normal. The diagnosis was amyotrophic lateral sclerosis. A similar condition in seven other family members was described to Dittel by the patient's relatives.

Schroeder[46] on reviewing 53 cases diagnosed as amyotrophic lateral sclerosis, described the familial aggregation of seven cases in three families. However, only the cases in one of the families would appear to be compatible with our definition of amyotrophic lateral sclerosis.

In that instance, two sisters noted the onset of symptoms at ages 48 and 46 years and developed the "classic picture of the Charcot form" prior to death three and one-half years after onset in each. In the older sister symptoms were first noted in the hands; in the other, symptoms began in the lower extremities. An aunt of these two was said to have had "typical amyotrophic lateral sclerosis." The patients' father died of tuberculosis at age 36 years and the mother died at age 77 years of arteriosclerosis. It is not stated whether the aunt was a sibling of the mother or of the father of the two sisters.

Barraquer-Ferré and Barraquer-Bordas[22] have recently described two families in Barcelona, Spain, in whom typ-

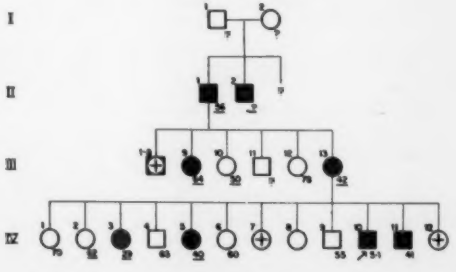


FIG. 10. Pedigree of German family in which amyotrophic lateral sclerosis occurred, after Dittel.[45]

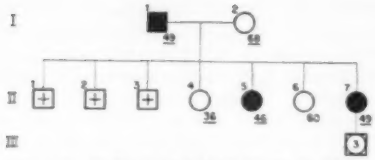


FIG. 11. Pedigree of Spanish family in which amyotrophic lateral sclerosis occurred, after Barraquer-Ferré and Barraquer-Bordas.[22]

ical amyotrophic lateral sclerosis was said to have occurred in more than one member of the family.

In the first family (figure 11) the father had died at age 49 years "with weakness of both legs and atrophy of both hands." His wife died at 68 years of age of a cerebral hemorrhage. They had seven children. The first three were males and died at early ages. The fourth child, a female, died when she was 36 years of age; the cause of her death is unknown. The fifth child "died at 46 years of age from an illness absolutely comparable with the one that killed the father: muscular atrophy and palsy of both lower limbs." The final cause of her death was "a bronchopulmonary infection." The sixth, another female, was 60 years old and in good health at the time of the report. The youngest was the patient whose condition was described in detail. She developed Aran-Duchenne type of atrophy in the upper extremities and shoulder girdle, more marked on the right than on the left; there were hyperactive reflexes in the upper extremities, particularly on the right side where Trömner's maneuver was positive. The deep reflexes in the lower extremities were slightly more hyperactive in the right than in the left side. Coordination and the results of sensory examinations were normal. Five months later "bulbar" symptoms were noted. The diagnosis was "amyotrophic lateral sclerosis, hereditary form."

The second pedigree (figure 12) illustrates the occurrence of the disease in a father and a son. The son, who was 65 years of age, was examined only once by the authors. One year before, he had noticed weakness in his calves which progressed to involve both lower limbs. At the time of examination the patient was bedridden and had a complete spastic paraplegia. Reflexes of the quadriceps were exaggerated, and Babinski's sign was present on both sides. There was slight amyotrophy of both hands, more marked on the left than on the right. The deep reflexes were somewhat exaggerated in the upper limbs; the abdominal and cremasteric reflexes were absent. The cranial nerves appeared to function normally. There was no sensory impairment or vesical dysfunction. Cerebrospinal fluid was normal.

This patient's father "died at the age of 72 years and his clinical picture was identical with his son's. The complete evolution of the syndrome took one year. The patient had only one daughter and she was in good health at the time of the examination." The patient died shortly after the authors had examined him; the diagnosis was "amyotrophic lateral sclerosis, hereditary form."

De la Vigne and Ali Ahmad[47] in 1952 reported the occurrence of typical amyotrophic lateral sclerosis in a 45 year old farmer named Amir (nationality not indicated), whose father had died of the same affliction at age 70 years.

The onset of progressive dysarthria and dysphagia had followed a "febrile period of one month." There was also progressive weakness and atrophy of the muscles of the hands, and later similar weakness occurred in the lower extremities.

The patient was examined two years after the onset of symptoms. Muscular atrophy and fasciculations were noted in the tongue and upper extremities; there was also marked weakness with wasting in the muscles of the face and in the intrinsic muscles of the hands, forearms, and shoulders. Spastic paraplegia with hyperactive reflexes and bilateral Babinski signs were present. The abdominal and cremasteric reflexes were present; sensation was intact.

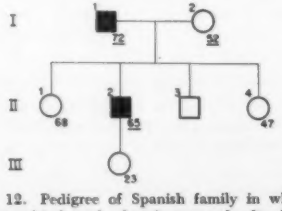


FIG. 12. Pedigree of Spanish family in which amyotrophic lateral sclerosis occurred, after Barraquer-Ferré and Barraquer-Bordas.[22]

Serologic reactions were negative for syphilis; spinal fluid showed 30 mg. of protein per 100 cc., 1 cell and normal colloidal gold curve.

The patient's father died at 70 years with an analogous history: one which evolved in the course of two years and which comprised paresis of the lower limbs, muscular atrophy in the upper limbs, atrophic hands, impotence, and difficulty in swallowing and articulation.

The patient's 20 year old son appeared free of any neurologic disorder. No other family history was given.

Robertson[13] reported the pedigree of the Scottish family illustrated in figure 13. The propositus developed progressive bulbar palsy at the age of 68 years and died one year later.

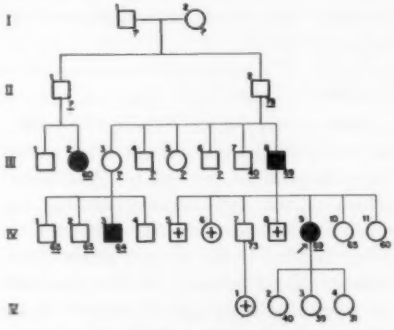


FIG. 13. Pedigree of Scottish family in which progressive muscular atrophy and progressive bulbar palsy occurred, after Robertson.[13]

In addition to dysarthria, dysphagia, and weakness of the facial muscles, there was also minimal spinal involvement in the form of slight atrophy of the thenar and hypothenar muscles of both hands. Coinciding with the onset of the bulbar palsy and showing "a similar, inexorable progression were intellectual defects of a type characteristically found in cortical atrophy or destruction."

At necropsy "the motor cortex showed diminution and atrophy of large pyramidal cells, with pigmentation in many of those remaining"; there were atrophy of the hypoglossal nuclei and the dorsal motor nuclei of the vagus and "moderate atrophy of anterior horn cells in the cervical and upper dorsal regions with pigmentation of surviving cells and astrocytic proliferation"; there was no demyelination of the columns of the spinal cord. "Frontal lobes: There was moderate loss of nerve cells, and many of those surviving showed brown lipochrome pigmentation. Argyrophile plaques were scattered throughout the cortex, but not in such numbers as to suggest senile dementia or Alzheimer's disease. Astrocytic proliferation (Cajal's stain) was seen in relation to many plaques, but diffuse gliosis was not present. Neurofibrillary tangles within nerve cells were not seen. The white matter was normal. There was no evidence of vascular or inflammatory disease."

The author discussed at length the signs of intellectual impairment in this case and those which have been occasionally reported in other cases of amyotrophic lateral sclerosis and contended that mental deterioration may, at times, be present on an organic basis and as an integral part of the syndrome.

Three other cases of typical progressive muscular atrophy and progressive bulbar palsy in the family are also described but in none was intellectual impairment a prominent feature. The pedigree is incomplete in some respects, since many of the persons referred to had emigrated from Scotland years before.

Dr. Leonard Dewey, in his interesting autobiography,[48] described his own symptoms of amyotrophic lateral sclerosis and indicated that his mother and probably his maternal grandfather as well had the disease (figure 14). Dewey and his mother both noted first symptoms at age 49 years. His mother had five siblings, all of whom died at age 70 years or later. One died with parkinsonism, one with cerebral hemorrhage, and the others had cardiac failure. The doctor himself was the only one affected of three children who survived to adulthood.

Rose and Stauffer[49] recently brought the following history of a New England

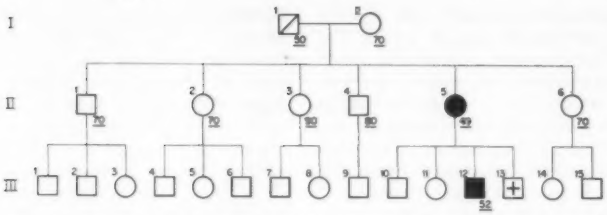


FIG. 14. Pedigree of U. S. family in which amyotrophic lateral sclerosis occurred, after Dewey.[45]

family, soon to be published in detail, to our attention:

Four siblings in one family have developed amyotrophic lateral sclerosis with bulbar palsy. The oldest, a male, first noted fasciculations of the upper limbs at age 49 years. There were progressive weakness and atrophy of the skeletal musculature; later, dysarthria, with involvement of bulbar musculature, developed. Cerebrospinal fluid was normal. The patient died five years after the onset of his first symptoms. The second sibling first noted difficulty in speaking and swallowing at age 61 years, following an upper respiratory infection. She developed severe atrophy of the tongue and inability to speak for many months prior to the development of severe weakness and atrophy of the skeletal musculature. Extensor plantar responses were noted. The duration was three years and one month and the clinical diagnosis of amyotrophic lateral sclerosis was confirmed by necropsy. The third sibling, a physician, noted fasciculations in the skeletal musculature beginning at age 61 years. These have been progressive but the patient's condition today is unknown since he has refused further medical attention. The youngest sibling, a female, noted the onset of dysarthria at age 52 years. Cerebrospinal fluid was normal. Symptoms were progressive, and weakness and atrophy of skeletal musculature beginning in the distal muscles of the extremities were noted. This patient developed spasticity with extensor plantar responses. She succumbed to her illness three years and three months after the onset of symptoms.

There was no known neurologic disease in earlier generations or in cousins. The mother died at age 79 years of a "stroke" and the father died at age 50 years of tuberculosis. It is not stated whether there were any unaffected siblings.

COMMENT

Most neurologists today consider amyotrophic lateral sclerosis as a disease which is not hereditary. The observation of the considerable familial aggregation of cases of this disorder on Guam has led to the present study. A review of the literature of the past 100 years reveals 18 pedigrees, many of three or more generations, which are compatible with dominant inheritance in amyotrophic lateral sclerosis and its clinical components, progressive muscular atrophy and progressive bulbar palsy. In the concluding section of this paper, to be published in the next issue of this journal, our own data on this subject will be presented, and the foregoing pedigrees and the reasons for the differing views on the role of heredity in amyotrophic lateral sclerosis will be discussed.

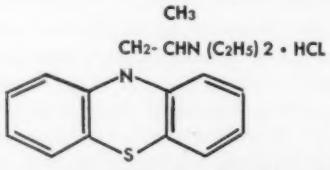
Parsidol in the Treatment of Parkinsonism

Dewey K. Ziegler, M.D. and Fernando Torres, M.D.

THE SYNTHETIC DRUG, diethylamino-2-propyl-1-N-phenothiazine, known in France and the United States by the name of Parsidol and in Great Britain by the name of Lysivane, has been reported as beneficial in alleviating manifestations of parkinsonism. This drug has been in use in Europe and Australia for a few years, and major benefit in diminution of muscular rigidity and in improvement of gait, posture, and expression has been reported.[1,6] Optimistic reports have recently come from this country.[2] The present study is an evaluation of the effectiveness of this agent on the various components of the parkinsonian syndrome, with control observations by the use of placebo.

PHARMACOLOGY

Parsidol has the following formula:



It is a white powder, with only slight water solubility. In experiments with dogs, moderate doses caused only slight transitory drop in blood pressure, the first real effect being ganglionic blockade, as shown by failure of heart and blood pressure to respond to repetitive stimulation of the peripheral end of the vagus. Other effects of the drug which may be important clinically are: 1) diminution of some acetylcholine effects, particularly bradycardia, hyperperistalsis, salivation; 2) nicotinolytic action; 3) anticonvulsant activity, probably attributable to central nervous system depression; 4) antihistamine activity (about one-tenth that of Phenergan); and 5) antispasmodic effect on the gut in the anesthetized dog and in the isolated intestine.

Acute toxicity in mice and rabbits consisted of convulsive movements, followed by complete loss of muscle tone and respiratory arrest. In dogs no weight loss or adverse effects on elements of the blood or any other organ were observed after prolonged administration of 25 mg./kg. five times weekly over a period of more than ten months.

MATERIAL AND METHODS

Thirty patients attending the outpatient department for parkinsonism were studied. There were 23 males and seven females, ranging in age from 30 to 72,

From the division of neuropsychiatry, Montefiore Hospital, New York City.

with the majority over age 50. All except a few of these patients had been ill for more than ten years, none less than two years. Eleven had a definite or suggestive history of a previous encephalitis. All patients had taken various combinations of drugs for months or years, usually trihexyphenidyl (Artane) and solanaceous drugs, either alone or in combination, and had shown a fairly static or downhill course with transient improvement in some cases.

Patients were seen at intervals of two to three weeks, and their course was observed over a period of six to nine months. On each visit the following were evaluated: 1) patient's subjective state —opinion concerning tremor and rigidity, changes in ability to perform daily tasks, and other beneficial or adverse effects; 2) tremor and rigidity, graded on a 1 to 4 scale; 3) gross condition of patient's facial expression and gait; and 4) dynamometry readings of strength in hands.

On each visit the patient was seen and examined by each of the authors separately, only one of whom was cognizant of changes in medication. The results of examinations were recorded each time without reference to previous examination.

All patients were started on placebo medication and after a variable period of time were shifted to Parsidol without their knowledge. Meanwhile the patients' previous medication was continued. Several who showed adverse psychologic reactions to placebo, and therefore to any medication, were eliminated from the series. In patients who showed some good results with Parsidol, medication was shifted back to placebos one or more times.

EFFECTS OF PLACEBO MEDICATION

Ten patients reported some adverse effects from placebos, five complaining of weakness and dizziness, two of gastric upset, and the others, accentuated tremor and rigidity. On the other hand, three patients reported some improvement on placebos alone. Further evaluation of drug effect was considered unreliable in this group of patients and they were eliminated from the study, leaving 17 patients for study.

EFFECTS OF PARSIDOL

Subjective changes. Twelve patients felt that they experienced definite improvement with Parsidol medication. Seven patients noted diminution of tremor, one noted less rigidity, three experienced diminution of both tremor and rigidity, and one patient ascribed benefit to a sedative effect. The remaining eight patients whose reports were considered reliable felt no improvement.

Objective changes. Thirteen patients showed some improvement on examination after Parsidol medication. Rigidity was less in two patients, tremor in four, and both were affected in seven. In all cases changes were slight, for example, a change of tremor or rigidity from severe to moderate or moderate to minimal.

Side effects of medication. Seven out of 17 patients reported some adverse effects from medication; all of these except one felt and showed over-all improvement. These consisted of restlessness in three patients, dizziness in two, and drowsiness in two. None complained of xerostomia or visual blurring.

Optimal dose. The optimal daily dose of those patients who showed improvement was 400 mg. or more in six patients,

300 to 400 in one, 200 to 300 in the remaining five. The daily dose was administered in four equal parts, after each meal and at night. Dosage was started at 20 to 50 mg. per day.

DISCUSSION

The number of patients showing either beneficial or toxic effects from placebo medication demonstrates the caution that must be exerted in evaluating a new drug in chronic conditions, particularly parkinsonism. Thirteen out of a total of 30 patients (43 per cent) reported some kind of change from placebo medication. Most of such patients are so suggestible that no conclusions can be drawn from their response to medication. With this group eliminated, subjective response proved to be a reliable clue to drug effect, either beneficial or not. It is striking that in ten out of 12 patients reporting subjective improvement, objective improvement was found on examination. We found, as have other observers,[3,4] that the patient's own evaluation of his course, supplemented by independent estimate by two observers of certain elements of neurologic disability (rigidity, tremor, facial expression, gait) was the most sensitive indication of response to medication. Although patients frequently complained of increasing weakness, dynamometry never showed change in values. Similarly, electromyography added little to observations on clinical examination.

Parsidol would seem to be a useful addition to the drugs available to patients with parkinsonism, since 13 of 17 fairly reliable patients showed some degree of improvement in tremor or rigidity or both. It should be emphasized again that the changes are rarely striking, and that this medication, like all others used for patients with this condition, is most effective in combination with other drugs. Two patients in this series were treated successfully with Parsidol alone, and all others were given Parsidol while their previous medication was continued.

The optimal dose in this series (about 400 mg. per day) was considerably in excess of that noted by other observers.[1,2] It was our experience that most patients who complained of adverse effects from these larger doses usually had the same effects from smaller ones, and frequently from placebos. There was no incompatibility of Parsidol given in combination with solanaceous drugs, Artane (trihexyphenidyl) or antihistaminics, but rather there appeared to be a synergistic action.

Leukopenia and agranulocytosis have been reported as a complication of therapy with Diparcol, another phenothiazine drug used in the treatment of parkinsonism.[5] White blood count was, therefore, checked at monthly intervals in all cases; but no marked hematologic changes were encountered in this small series.

SUMMARY AND CONCLUSIONS

1. The effect of diethylamine-2-propyl-1-N-phenothiazine (Parsidol) on various manifestations of parkinsonism was evaluated in a series of 30 patients.

2. Treatment with the medication was alternated with administration of placebos. Thirteen patients reported some marked type of effect from placebo (adverse in ten cases) and were considered unsuitable for further drug testing.

3. Of the remaining 17 patients who showed no reaction to placebo, 13 showed some improvement upon addition of Parsidol to their previous therapeutic

regimen. Objective improvement tended to parallel subjective, and affected both tremor and rigidity.

4. In this group of cases, Parsidol seemed a valuable addition to the management of parkinsonism.

Information on the pharmacologic properties of Parsidol is by courtesy of unpublished material by John F. Reinhard of Warner-Chilcott Laboratories. The Warner-Chilcott Laboratories also kindly supplied the Parsidol and placebos used in this study.

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■ If the palpitation and the attendant weakness of the limbs be considered as to the order in which the several parts are attacked, it is believed, that some confirmation will be obtained of the opinion which has been just offered, respecting the cause, or at least the seat, of that change which may be considered as the proximate cause of this disease.

One of the arms, in all the cases which have been here mentioned, has been the part in which these symptoms have been first noticed; the legs, head, and trunk have become gradually affected, and lastly, the muscles of the mouth and fauces have yielded to the morbid influence.

The arms, the parts first manifesting disordered action, of course, direct us, whilst searching for the cause of these changes, to the brachial nerves. But finding the mischief extending to other parts, not supplied with these, but with other nerves derived from nearly the same part of the medulla spinalis, we are of course led to consider that portion of the medulla spinalis itself, from which these nerves are derived, as the part in which those changes have taken place, which constitute the proximate cause of this disease.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Radioisotope Studies in Neuromuscular Disease

2. Studies in Muscular Dystrophy and Myotonia Dystrophica with Sodium^{22} and Potassium^{42}

William H. Blahd, M.D., Franz K. Bauer, M.D.
Raymond L. Libby, Ph.D. and Augustus S. Rose, M.D.

PRELIMINARY isotope studies in various neuromuscular disease states have demonstrated a diminution of body potassium in patients with muscular dystrophy and myotonia dystrophica.[1] The present investigation, a continuation of earlier studies, has been broadened to include the study of selected family members of muscular dystrophy patients. In addition, the body sodium content has been determined by isotope methods in order to better understand other aspects of electrolyte metabolism in primary muscle disease.

The data have been obtained from a study of 33 patients with muscular dystrophy and myotonia dystrophica and 38 family members of patients with muscular dystrophy.

In the present study, the exchangeable potassium and sodium content of the body was determined with the radioactive isotopes potassium^{42} and sodium^{22} by the method of isotope dilution as described by Corsa and co-workers,[2] and Forbes and Perley.[3] Values in man, as estimated by these authors, indicate that approximately 82 per cent of the total body sodium and 95 per cent of the total body potassium are measured by this method. The quantity of an element which will exchange with its isotope is termed the body content of exchangeable element, which, in the case of complete exchange, is the total amount of element in the body. Although the measurement of the exchangeable sodium and potassium of the body does not correspond to the total body content, it does reflect the physiologically active or available amount of these elements.

PROCEDURE AND METHODS

Radioactive potassium^{42} (300 microcuries) was given orally immediately following the intravenous administration of sodium^{22} (20 microcuries). Blood samples were taken at one and 29 hours for counting and sodium analysis. All urine specimens were collected and pooled. The specific activity of the urine was determined from 30-hour spot samples. In addition, 24 hour urinary creatine and creatinine excretion was meas-

From the radioisotope unit, Wadsworth General Hospital, Veterans Administration Center, Los Angeles, California, and the departments of medicine and radiology, School of Medicine, University of California at Los Angeles.
This study was aided by funds from the Muscular Dystrophy Associations of America, Inc.
Read in part at the meeting of the American Neurological Association, Atlantic City, June 14, 1954.

ured. No restrictions were placed on activity or the intake of food or water.

All radioactive materials were counted in the liquid state with a thallium-activated sodium iodide crystal scintillation well counter.[4] Urine samples were counted within 40 hours after administration of the tracer materials and then recounted three days later. The differential decay rates of potassium42 (12.4 hours) and sodium22 (2.6 years) facilitated the independent measurement of these isotopes in the same biologic sample and made possible the simultaneous determination of exchangeable sodium and potassium.

The sodium and potassium concentrations of blood and urine samples were determined by flame photometry.[5] Urinary creatine and creatinine concentrations were determined by a modification of the Folin and Wu method.[6]

The exchangeable sodium and potassium was then calculated from these data according to the following standard isotope dilution equation:

$$E = \frac{Ci - Co}{(Cf)/(E)}$$

E – amount of exchangeable body electrolyte (meq.)
Ci – total amount of administered radioisotope (units).
Co – total amount of excreted radioisotope (units).
(Cf) – concentration of radioisotope found in the body fluid (units/L).
(E) – concentration of naturally occurring electrolyte in body fluid (meq./L).
(Cf)/(E) – equilibrium specific activity (units/meq).

TABLE 1

Patient	Age	Height (cm)	Weight (Kg)	Exchangeable K (meq)	Ke/Wt (meq/Kg)	Exchangeable Na (meq)	Nae/Wt (meq/Kg)	Intracellular Na (meq)	Extracellular Na (meq)	Creatine (Gm/24Hr)	Creatinine (Gm/24Hr)	Physical Disability
MUSCULAR DYSTROPHY—MALE												
E. K.	33	183	101.1	2798	27.6	3335	32.9	876	2459	1.65	0.87	2+
L.G.	33	183	88.3	2070	23.4	3059	34.6	692	2367	1.28	0.75	2+
F.S.	39	184	84.8	1554	18.3	3076	36.2	831	2245	0.61	0.51	3+
M.B.	60	175	84.0	2450	29.1					0.41	1.15	1+
R.S.	32	179	77.2	2125	27.5	3130	40.5	1505	1635	1.03	1.15	2+
W.F.*	34	183	76.8	1197	15.6	3412	44.4	991	2421	0.70	0.48	3+
C.D.	36	173	74.0	2359	31.8	2586	35.0	647	1939	0.17	1.07	1+
J.V.	34	180	74.0	2141	28.9	2994	40.5	836	2158	0.50	0.90	1+
A.F.	48	168	71.2	2240	31.5	2800	41.2	1815	985	0.34	1.02	2+
L.R.*	21	173	69.8	1132	16.2					0.37	0.48	3+
S.T.	31	168	66.4	2266	34.1	2930	44.2	1045	1885	0.34	1.26	1+
W.P.*	30	175	65.9	1239	18.6	2190	33.2	505	1685	0.88	0.29	3+
R.M.*	19	160	64.3	1236	19.2					0.91	0.55	3+
B.H.	32	170	61.4	1921	31.3	2390	39.0	755	1635	0.42	0.99	2+
J.K.*	16	173	55.9	2179	31.8	2963	43.2	517	2446	0.49	0.78	3+
S.S.*	14	165	52.3	1400	26.9	2420	46.3	710	1710	0.59	0.63	3+
M.R.	21	160	49.6	2182	43.5							1+
R.W.*	25	168	39.0	782	20.0					0.61	0.20	3+
Mean	31.1	173	69.8	1863	26.7	2868	39.3	902	1966	0.67	0.76	
Range	14-60	160-184	39.0-101.1	782-2798	15.6-43.5	2190-3412	32.9-46.3	505-1815	1625-2459	0.17-1.65	0.29-1.26	
MYOTONIA DYSTROPHICA—MALE												
L.E.	32	175	70.9	2832	39.9					0.25	1.11	1+
R.M.	26	173	70.0	2827	40.2							1+
E.J.	33	178	66.8	2453	36.7					0.18	0.96	1+
C.G.	54	170	63.4	1709	26.8					0.20	1.20	2+
J.L.	39	160	63.1	1603	25.4					0.07	0.76	1+
T.C.	57	170	59.4	1875	31.5					0.27	0.79	2+
M.W.	52	158	53.6	1742	32.5					0.11	0.85	1+
G.B.	44	168	53.6	1958	36.5					0.17	0.91	1+
W.I.	32	165	51.9	2366	45.6					0.32	1.25	1+
C.M.	49	155	46.0	1740	7.8					0.05	0.72	1+
Mean	41.8	167	59.9	2110	34.5					0.18	0.95	
Range	26-57	155-178	46.0-70.9	1603-2832	25.4-45.6					0.05-0.32	0.72-1.25	
NORMAL MALES†												
Mean	33.8	175	74.7	3557	48.2	3277	43.5	822	2463	0.18	1.71	
Range	17-62	165-188	63.6-88.6	2825-4554	39.8-62.3	2670-3767	37.8-47.5	530-1480	1970-3003	0.002-0.34	1.23-2.11	

*Onset of disease during the 1st decade of life.
†All values are based on determinations in 23 normal subjects.

The one-hour dilution of sodium22 was taken as a gross indication of the volume of extracellular sodium.[7] Intracellular sodium was calculated as the difference between exchangeable sodium and extracellular sodium.

RESULTS

The results of this study are summarized in tables 1 and 2. Without attempting to establish a scheme of classification, the patients with muscular dystrophy were, arbitrarily and for convenience, further separated into two groups: childhood muscular dystrophy, with onset of the disease in the first decade of life; and adult muscular dystrophy with onset after the first decade.

Exchangeable potassium. The exchangeable potassium values obtained in the cases of childhood muscular dystrophy were the lowest. In seven such male patients, exchangeable potassium ranged from 782 to 2179 meq. with a mean value of 1309 meq. The ratio between exchangeable potassium and body weight was 21.8 meq. per kilogram (table 3). Low exchangeable potassium levels were observed also in two female patients with childhood muscular dystrophy (table 3). Cases of adult muscular dystrophy showed less diminution of exchangeable potassium. The range in the male patients was 1554 to 2798 meq., with a mean value of 2216 meq. and a mean exchangeable potassium to weight ratio of 29.9 meq. per kilogram. In adult female muscular dystrophy patients, the mean was 1516 meq., with a range of 1157 to 1715 meq. The mean value for Ke/Wt ratio was 24.7 meq. per kilogram. Although these

TABLE 2

MUSCULAR DYSTROPHY—FEMALE

Patient	Age	Height (cm)	Weight (Kg)	Exchangeable K (meq)	Ke/Wt (meq/Kg)	Exchangeable Na (meq)	Nae/Wt (meq/Kg)	Intracellular Na (meq)	Extracellular Na (meq)	Creatine (Gm/24Hr)	Creatinine (Gm/24Hr)	Physical Disability
E.K.	58	168	63.6	1157	18.2					0.61	0.35	3+
J.T.	27	170	63.2	1677	26.4	2162	34.2	522	1640	0.33	0.78	2+
V.F.	43	158	58.2	1715	29.5	2034	35.0	204	1830	0.30	0.90	1+
B.H.*	27	160	57.5	718	16.2	2285	39.8	422	1863	0.27	0.93	1-2+
M.M.*	20	158	49.5	880	17.8	2144	43.3	495	1649	0.27	0.65	1-2+
Mean	35	163	58.4	1229	21.6	2156	38.1	411	1746	0.36	0.72	
Range	20-58	158-170	49.5-63.6	718-1715	17.8-29.5	2034-2285	34.2-43.3	204-522	1640-1863	0.27-0.61	0.35-0.93	

NORMAL FEMALES†

Mean	24.6	163	56.5	2406	43.1	2395	39.5			0.18	1.20	
Range	21-36	150-178	43.6-77.3	1905-3148	38.5-54.4	2153-2913	35.7-41.6			0.03-0.32	0.98-1.39	

*Onset of disease during 1st decade of life.
†Values based on determinations in 10 normal subjects. The exchangeable sodium data obtained from Forbes and Perley.[3]

TABLE 3

	EXCHANGEABLE POTASSIUM (meq.)		Ke/Wt (meq./Kg.)	
	Range	Mean	Range	Mean
*Childhood muscular dystrophy—male	782-2179	1309	15.6-36.3	21.8
Adult muscular dystrophy—male	1554-2798	2216	18.3-43.5	29.9
Normal males	2825-4554	3587	39.8-62.6	48.2
*Childhood muscular dystrophy—female	718-880	799	16.2-17.8	17.0
Adult muscular dystrophy—female	1157-1715	1516	18.2-29.5	24.7
Normal females	1905-3148	2406	38.5-54.4	43.1

*Onset of disease during the 1st decade of life.

results were higher than those obtained in the cases designated childhood muscular dystrophy, they were well below the levels obtained in normal males and females (table 3).

All of the cases of myotonia dystrophica that were studied had significantly depressed exchangeable potassium. The mean value was 2110 meq. and the range, 1603 to 2827 meq. More than one half of these patients had exchangeable potassium levels below 2000 meq., or a reduction of approximately 40 per cent.

The actual distribution of exchangeable potassium values in the above cases (male patients) is illustrated in figure 1. It is readily apparent that despite the wide range of exchangeable potassium in patients with muscular dystrophy and myotonia dystrophica, none of these values extend above the range obtained in normal subjects. The bulk of the results obtained in these cases are well below normal.

Exchangeable sodium. Exchangeable sodium in 13 male patients with muscular dystrophy ranged from 2190 to 3412 meq. The mean of 2868 meq. was lower than the normal mean of 3277 meq. A corresponding depression of the exchangeable sodium to weight ratio was also observed; 39.3 meq. per kilogram as compared to the normal 43.5 meq. per kilogram (table 1). A similar slight depression of exchangeable sodium was observed in four female muscular dystrophy patients (table 2).

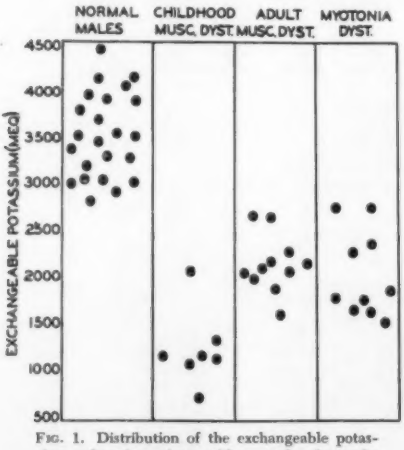

FIG. 1. Distribution of the exchangeable potassium values in patients with muscular dystrophy and myotonia dystrophica.

Intracellular sodium was within the limits of the normal range in all muscular dystrophy patients. Extracellular sodium levels, however, were below the lower limits of normal in more than half of the cases (table 1).

Exchangeable potassium of parents and siblings of muscular dystrophy patients. Exchangeable potassium values obtained in parents and unaffected, healthy siblings of muscular dystrophy patients were within the normal range with three exceptions. Three unrelated individuals in a group of 14 healthy male siblings had exchangeable potassium levels below 2000 meq. Two were apparently normal, healthy males, 14 and 20 years of age. The third was a 25 year old day laborer who had skin changes suggestive of scleroderma.

Serum sodium and potassium. None of the patients or family members studied had abnormal serum sodium or potassium levels.

Creatine - Creatinine. The 24 hour urinary creatine excretion was increased in all muscular dystrophy patients (tables 1 and 2). The mean values were 0.67 gm. in the male patients and 0.36 gm. in the female patients as compared to the normal means of 0.18 gm. Twenty-four hour urinary creatinine excretion was reduced in all cases of muscular dystrophy to mean values of 0.76 gm.

in male patients and 0.72 gm. in female patients (normal means: 1.71 gm. and 1.20 gm. respectively).

The patients with myotonia dystrophica exhibited no creatinuria. The mean 24 hour urinary creatine excretion was normal (0.18 gm.). The mean 24 hour urinary creatinine excretion was 0.95 gm. as compared to 0.76 gm. in patients with muscular dystrophy and 1.71 gm. in normal subjects (table 1).

DISCUSSION

Correlation between exchangeable potassium, 24 hour urinary creatinine, and physical disability. In the majority of patients with muscular dystrophy, physical disability was proportional to the level of exchangeable potassium. There was a similar close correlation with the 24-hour urinary creatinine excretion. Figure 2 illustrates the correlation between exchangeable potassium, creatinine excretion, and physical disability in the male patients. These data were grouped arbitrarily according to the degree of pathologic involvement. The cases falling into the 1+ category showed only minimal disability and relatively high exchangeable potassium and creatinine excretion. The patients in the next group manifested moderately disabling disease and correspondingly diminished exchangeable potassium and creatinine excretion. In the last category, designated 3+, were patients with severe disability. Both exchangeable potassium and creatinine excretion were markedly depressed. This group was composed entirely of patients with childhood muscular dystrophy.

Although exchangeable potassium and physical disability could be correlated in most cases, there were a number of instances where this relationship did not apply. More than one half of the patients with myotonia dystrophica had exchangeable potassium levels below 2000 meq., yet none exhibited the severe physical disability associated with comparably reduced exchangeable potassium levels observed in childhood or adult muscular dystrophy. The marked depression of exchangeable potassium observed in two sisters who had childhood muscular dystrophy was associated with considerably less physical disability than patients with adult dystrophy who had much higher levels of exchangeable potassium. Finally, the most striking contradictions to the usual relationship between exchangeable potassium and muscle function were observed in the three uninvolved male siblings of muscular dystrophy patients, who showed no evidence of muscle disease yet had extremely low exchangeable potassium levels.

A similar type of disparity existed between 24 hour urinary creatinine excretion and exchangeable potassium. Although there was good correlation between creatinine excretion and exchange-

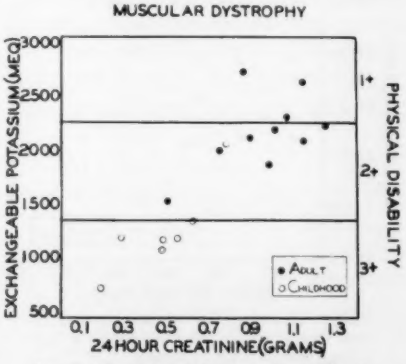

FIG. 2. Correlation between exchangeable potassium, 24 hour creatinine excretion, and physical disability in male patients with muscular dystrophy.

able potassium in most cases, patients who had myotonia dystrophica with markedly diminished exchangeable potassium exhibited considerably higher creatinine excretion than muscular dystrophy cases with comparably lowered potassium values. The most marked disparity between exchangeable potassium and creatinine excretion was noted in three siblings of muscular dystrophy patients who, despite significantly lowered potassium levels, had normal 24-hour urinary creatinine excretion.

Distribution of sodium[22]. Exchangeable sodium values, though somewhat lower than normal in some cases, for the most part fell within the normal range. There seemed to be a remarkably good correlation between body weight and exchangeable sodium, in contradistinction to potassium. Figure 3 illustrates the relationship between exchangeable sodium and potassium and body weight in male patients with muscular dystrophy. The positive correlation of sodium and the negative correlation of potassium to body weight is apparent.

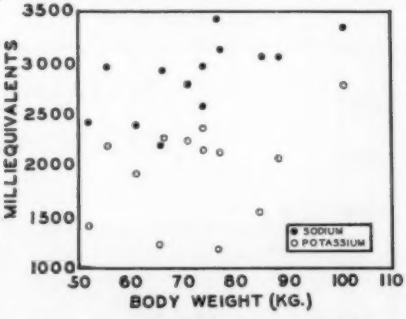

FIG. 3. Correlation between exchangeable sodium and potassium and body weight in male patients with muscular dystrophy.

Neither the age of onset of muscular dystrophy nor the extent of physical disability had any apparent influence upon exchangeable sodium levels or the intracellular-extracellular distribution of sodium. Patients with childhood dystrophy who manifested severe disability had both normal exchangeable sodium levels as well as essentially normal distribution of sodium. Extracellular sodium was below the normal range in some cases. The explanation of this discrepancy is not certain. It may be related to indeterminate errors associated with the one-hour sodium[22] dilution method or the more extensive over-all weight range of the patients as compared to the controls.

Theoretical considerations. Considerable importance is attributed to the role of potassium in normal muscle function, yet its mode and site of action is essentially unknown. The data obtained from these exchange studies suggest that there may be a gradual and progressive lowering of body potassium during the early stages of certain primary muscle diseases. This may be due to an inherent intracellular defect resulting in the gradual leakage of cellular potassium and its subsequent renal loss from the body. The loss of potassium from the cell is followed by a compensatory intracellular accumulation of sodium and water.[8] The failure of the usual homostatic mechanisms to readjust the internal environment of the cell may then lead to its ultimate destruction. The fact that intracellular sodium was found to be normal or slightly elevated when both exchangeable and extracellular sodium levels were below normal may actually indicate a relative increase in cellular sodium. This would lend support to the concept of a compensatory increase in sodium following the loss of cellular potassium.

Whether such changes are precedent to the disease or simply a concomitant phenomenon is not known. The low potassium values observed in three uninvolved male siblings of muscular dystrophy patients suggest the former possibility; however, prolonged observation will be necessary to confirm this point. On the other hand, it is conceivable that these unusual findings may represent a benign biochemical trait. This strange lack of correlation between exchangeable potassium and physical disability suggests that there may be a critical level of body potassium below which normal muscle function is no longer maintained, resulting ultimately in muscular atrophy and degeneration.

These ideas are mainly conjectural, but may help to explain some of the findings and discrepancies in this study and indicate the direction of further investigation.

SUMMARY

1. Measurements of total exchangeable sodium and potassium by the isotope dilution method (utilizing radioactive sodium22 and potassium42) were performed in patients with muscular dystrophy and myotonia dystrophica and family members.

2. Exchangeable potassium was diminished in muscular dystrophy and myotonia dystrophica. The lowest values occurred in patients with childhood muscular dystrophy.

3. Exchangeable sodium was not significantly depressed; most values fell within the normal range. Intracellular sodium was normal, whereas extracellular sodium levels were slightly depressed.

4. Abnormally low exchangeable potassium values were obtained in three healthy male siblings of muscular dystrophy patients. Values obtained in parents and other siblings were within the normal range.

5. Creatinuria was observed in all cases with the exception of the patients with myotonia dystrophica. Creatinine excretion was decreased in all patients.

6. There was good correlation between exchangeable potassium, creatinine excretion, and physical disability in most patients with muscular dystrophy and poor correlation in most patients with myotonia dystrophica.

7. The possibility of a critical level of body potassium is suggested, below which normal muscle function cannot be maintained, resulting ultimately in muscular atrophy and degeneration.

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CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D. Section Editor
with the assistance of E. P. Richardson, Jr., M.D.

Presented by *Helena E. Riggs, M.D., Charles Rupp, M.D. and Lewis Barness, M.D.*

CASE PRESENTATION

A 13 month old colored male infant was admitted to the hospital on March 8, 1954, because of paralysis of the right arm and leg. He had been born at full term, was breast fed, and showed normal development. He had had chickenpox one month before hospitalization and recovered after two weeks. One week before admission the child started vomiting about three times a day and he was fretful. On the day of admission the right arm and leg appeared to be paralyzed. He had had no convulsions and had not lost consciousness.

Physical examination showed an active child who did not move his right arm or leg. Extraocular movements were full. There was drooping of the right side of the face and slight voluntary stiffness of the neck. Right posterior cervical adenopathy was noted. The ear drums were normal and there was no discharge. Macules of the previous exanthem were still present. There was no evidence of trauma to the head.

Neurologic examination showed that the right face, arm, and leg were paralyzed, with increased reflexes, Babinski sign, and ankle clonus. Pinprick sensation was impaired on the right side.

Laboratory studies: Urinalysis was negative. Blood studies showed a red cell count of 4.30 million and a white count of 10.6 million. The Mantoux skin test was 1+ positive. The spinal fluid was clear, under normal pressure, with no cells, and protein of 68 mg./100 cc.

Course: There was little change in the child's condition during the first ten days. Two weeks after admission he developed a stiff neck and retraction of the head. Slight ptosis of the left lid was noted, and the hemiplegia became more spastic. Rales were present in the chest. The spinal fluid showed a pressure of 180 mm./H_2O; a white cell count of 200 with 60 per cent polymorphonuclear cells and 40 per cent lymphocytes; sugar 40 mg./100 cc.; chlorides 692 mg./100 cc.; and protein 85 mg./100 cc. The child became restless and irritable, and vomited after feedings. Repeated generalized convulsions and a bilateral Babinski sign developed two days before death on April 4, 1954. A final spinal tap showed blood tinged fluid, a pressure of 250 mm., 550 red cells, and 300 white cells of which 90 per cent were lymphocytes.

DISCUSSION

DR. TURNER (Medical resident): I believe the child had tuberculous meningitis. He had a positive skin test which, at 13 months, means an active disease process. The spinal fluid findings are compatible with tuberculosis, though not absolutely diagnostic.

DR. RAY (Neurologic resident): The child could have had a tuberculoma in the left cerebral hemisphere with a later meningeal spread. I believe that tuberculous

From Philadelphia General Hospital, Philadelphia.

meningitis often appears after a febrile illness, such as measles or pertussis.

DR. MELGAARD (Pediatric resident): I believe the primary lesion was an intracerebral tuberculoma, and in the course of the disease, there was a meningeal spread.

DR. DELAPLAINE (Neurologic resident): Tuberculosis would seem to be the most obvious cause, but several things militate against it. One might expect a more strongly positive skin test in tuberculous meningitis. The history of chickenpox should not be disregarded completely. Do the macules of chickenpox remain for such a long time?

DR. MILLER (Pediatric resident): The child may have had a tuberculoma deep in the cortex on the left with later extension to the other side. The whole picture could be that of an abscess with meningeal extension, although the ears were negative and the lungs were presumably clear.

DR. BAKER (Pediatric resident): I was considering the possibility of chickenpox encephalitis. The time interval between the onset of chickenpox and onset of the neurologic disease is long, but it can be as long as 30 days.

DR. BARNESS (Chief of pediatric service): At first chickenpox encephalitis looks like a possible diagnosis. In answer to Dr. Delaplaine's question, we frequently see the rash, or the residua of the rash, present for a year after acute chickenpox. It is a rather unusual course for chickenpox encephalitis, however; the time of onset, as Dr. Baker has pointed out, is rather late for chickenpox encephalitis to develop. The course in chickenpox encephalitis is generally much more fulminating. It is one of the worst demyelinating encephalitides that we see. In contrast to what is stated in some textbooks, it is much more severe than that of measles. Today, we see very few acute bacterial meningitides and relatively few that progress like this. If we have a positive skin test even though it is only 1+ (I will talk about that in a minute) it is tuberculosis until proved otherwise. I would not be too disturbed about a 1+ Mantoux skin test because there may be an anergy of the skin in severely ill children, especially in tuberculosis. The only other condition that I would consider seriously is a brain abscess from the left mastoid area. A subdural abscess in that area giving supratentorial pressure could give you this picture.

DR. RIGGS (Chief of division of neuropathology): Would you comment on the terminal picture of repeated generalized convulsions and bilateral Babinski, with the spinal fluid showing an increasing pressure and 300 white cells with 90 per cent lymphocytes?

DR. BARNESS: Blood tinged spinal fluid may be due to a traumatic tap. In a 13 month old child who has been convulsing for two days, it would be very difficult to do an atraumatic tap. The other spinal fluid findings are compatible either with tuberculosis or with a mass lesion close to the meninges.

DR. RIGGS: In adults we put a great deal of faith on decrease in the spinal fluid chlorides as indicative of tuberculous meningitis. Is that true also in children?

DR. BARNESS: We have not been paying as much attention to that recently. Even though the spinal fluid chlorides do not exactly mimic the serum chlorides, the relationship to serum chloride is so close that, if the child is dehydrated, you would expect a normal or as high spinal fluid chloride as serum chloride, and if the child has been losing salt, then both spinal fluid and serum chlorides are low. Tuberculous meningitis causes a tremendous amount of vomiting so the serum chloride becomes low, and this reduction is reflected in the spinal fluid chloride.

DR. RIGGS: Is spinal fluid sugar as low in tuberculous meningitis in children as it is in adults?

DR. BARNESS: Yes, I think you must pay a great deal more attention to the level of sugar than of chlorides.

DR. RIGGS: Is lymphocytic infiltration

present in chickenpox encephalitis, or is there primary demyelinization without inflammatory reaction?

DR. BARNESS: I do not remember much inflammatory reaction in the one autopsy I saw.

DR. TURNER: Brain makes the statement that chickenpox encephalitis is a demyelinating disease, and that there is local perivascular round cell infiltration as well as infiltration at a distance from the vessel. He also states that chickenpox encephalitis in England is a benign condition and that complete recovery occurs in over 90 per cent of their cases.

DR. BARNESS: In my limited personal experience, the worst form of encephalitis I have ever seen followed chickenpox, and the most benign, mumps, with measles somewhere in between.

DR. RIGGS: One possible explanation is that the clinical and pathologic picture may vary from epidemic to epidemic and in different localities. The first case I saw was in 1929. The child apparently recovered neurologically, but had to be institutionalized because of changes in behavior.

DR. RUPP (Visiting chief of neurology): In this hospital we do not see much chickenpox encephalitis. I remember only two cases with residual neurologic and personality damage. How frequent is chickenpox encephalitis, Dr. Barness?

DR. BARNESS: It is extremely rare. The incidence is less than one per cent.

DR. RUPP: It may be interesting to review the clinical course of this patient. We have an infant who first began to vomit, and then a few days later developed a right sided paralysis. The first spinal tap revealed only increased protein, findings which suggest an intracranial mass lesion. In time he developed meningeal signs, became more spastic, and the spinal fluid showed an increased cell count. The spinal fluid protein rose and the child continued to vomit. While the spinal fluid findings are not pathognomonic of tuberculous meningitis, they certainly do not exclude it. A number of diagnoses have been suggested, one is that of postchickenpox encephalopathy. I agree with what has been said against this diagnosis. In this case the symptoms came on late after the acute course. One would expect in a chickenpox encephalitis that meningeal signs would predominate at the start. How can one explain the symptoms of a mass lesion which were the first manifestation? The spinal fluid findings are not helpful.

We know the child was tuberculous, and he was of a racial group prone to develop tuberculosis. A tuberculoma with a meningeal spread would explain most of the symptoms. Again, however, the spinal fluid findings are not pathognomonic; the last spinal fluid was bloody with 300 white cells and 550 red cells. One would expect that all those white cells were not due just to the blood; quite likely there was some lymphocytic reaction due to infection. A tuberculoma in the left cerebral hemisphere with a meningitic spread would be a strong diagnostic possibility.

A brain abscess with subsequent leakage of pus into the meninges could explain the picture, but there is nothing in the protocol to suggest a primary source, such as infection in the mastoid, the sinuses, or in the lungs. There is one possibility which is rather remote. The infant first had a right sided weakness; spinal tap was negative at the start. There was a little weakness of the right side of the face, some ptosis of the eyelid. The patient was only 13 months of age, he was sick and probably not too cooperative. It was undoubtedly difficult to examine the cranial nerves, and one wonders if there might have been a peripheral type of facial palsy. Some years ago we studied some cases of medullary tumors in which there was vomiting and symptoms of irritation of the meninges. Various clinical diagnoses were suggested, such as tuberculous meningitis, but at necropsy the patients were found to have a tumor in the lower pons or the medulla. We do not have any definite evidence for such a diagnosis

here, but I think it is worthy of comment. In summary, I think the most likely diagnosis is a tuberculoma with a secondary meningeal spread.

DR. BARNESS: There is one other condition we should consider if only to rule it out, and that is chronic lead poisoning. Any 13 month old child who has a history of vomiting followed by paralysis should be studied for possible chronic lead poisoning. At 13 months of age the child is able to get around and is able to chew paint. Many inside paints are made with lead. Two things are against lead poisoning – first, the urine was negative and the red count was normal, and second, the sugar in the spinal fluid was low. Usually in chronic plumbism we have an anemia, some sugar in the urine, and a high spinal fluid sugar.

DR. RUPP: Would you expect lymphocytosis of the spinal fluid in lead encephalopathy?

DR. BARNESS: We have recently seen one child who had a lymphocytosis with normal spinal fluid pressure and an elevated protein.

DR. RUPP: After a number of spinal taps, an aseptic meningitis with lymphocytic outpouring may occur as a result of trauma and introduction of air, but in my experience the cell count in a typical lead encephalopathy is not usually increased – although, as you say, the sugar is often increased.

DR. RIGGS: I might say here that Hassin mentioned a lymphocytic reaction in the brain in lead encephalopathy, as did Foley. I have never seen an inflammatory reaction in the cases autopsied here.

DR. SCOTT (Medical resident): Is the clinical picture at all compatible with congenital lues?

DR. RUPP: It is an early age for congenital neurolues. How are you going to explain the hemiplegia with the initially negative spinal fluid?

DR. RIGGS: Isn't congenital syphilis more apt to be visceral in children this young?

DR. BARNESS: Yes, you would expect liver and spleen pathology.

DR. RIGGS: To summarize the necropsy findings, the brain showed a very limited focal tuberculous meningitis around the base, and a small tuberculoma in the left hemipshere involving the subcortical white matter of the motor corona. The tuberculoma was old but there was a relatively recent direct extension of the tuberculous process from the granuloma into the interpeduncular cistern. The child also had miliary tuberculosis. We assumed that at some earlier period, primary seeding of the brain had given rise to this tuberculoma which caused the hemiplegia, and that later the tuberculoma spread to the subarachnoid space producing a localized tuberculous meningitis, and possibly the miliary visceral spread as well. The child had been vomiting and became dehydrated. As a result, shortly before death a marantic thrombus formed in the longitudinal sinus causing hemorrhage into the paracentral lobules of both sides, accounting for the generalized convulsions and for the bilateral Babinski sign. The pathologic diagnosis, then, is tuberculoma of the left cerebral hemisphere with secondary miliary spread; terminal marantic thrombosis of the longitudinal sinus with hemorrhage into the brain.

DR. BARNESS: In a tuberculous meningitis or tuberculoma does endarteritis occur either locally or generalized?

DR. RIGGS: If patients with tuberculous meningitis are treated with streptomycin and live long enough, it very frequently does. The endarteritis is not specific for tuberculosis, but may occur in any chronic meningeal infection. Under such conditions the endarteritis is usually localized to those areas with residual inflammatory reaction.

DR. RUPP: May I ask, do we still see many marantic sinus thromboses?

DR. RIGGS: Not in children. We are more apt to see them in patients with acute mania in very hot weather. I believe they are due in large part to dehydration. Their absence in infants and children probably reflects the greater attention paid to electrolyte and fluid balance.

CASE REPORT

Neurologic Manifestations of Postpartum Pituitary Insufficiency

Thomas W. Farmer, M.D. and Charles A. Flowers, Jr., M.D.

EPISODES OF UNCONSCIOUSNESS and periodic convulsions occur subsequent to postpartum pituitary insufficiency. It is of importance to understand the etiology of this characteristic syndrome in order that endocrine therapy may be instituted in this disabling and eventually fatal disorder.

Simmonds[1] in 1914 first described clearly the clinical picture associated with severe destruction of the anterior lobe of the pituitary gland. This syndrome is related to the secondary atrophy of the gonads, the thyroid, and the adrenal glands. Destructive lesions producing this clinical syndrome include ischemic necrosis, fibrosis, tumor, and granuloma. Of these necrosis is by far the most common cause of the disease. The vast majority of cases of necrosis are due to infarction occurring after severe hemorrhage in the puerperium. This relationship was noted by Simmonds in the first cases which he described. However, the direct relationship of this syndrome to hemorrhage following obstetric delivery has been greatly amplified by Sheehan.[2–4] He has shown that areas of necrosis of the anterior pituitary gland of varying size are commonly found in women dying after postpartum hemorrhage. Small thrombi in the sinuses of the anterior lobe were demonstrated in the region of necrotic areas of the anterior pituitary gland. The explanation of the pathogenesis of the infarct suggested by Sheehan and Murdoch[5] is as follows: "At a normal delivery there is presumably a physiological reduction of the blood flow to the anterior lobe; if in addition to this there is a severe general circulatory collapse, it is possible that the blood flow to the anterior lobe may be so reduced that thrombosis occurs in the vessels of the lobe and leads to ischemic necrosis."

Of 92 proved cases summarized by Farquharson,[6] 39 were due to puerperal ischemic necrosis; 31 were due to fibrosis and necrosis due to other causes; 14 were due to tumors, of which seven were craniopharyngiomas; and eight were secondary to chronic granuloma.

Pathologic studies have shown that when the remnant of the anterior pituitary gland constitutes more than one-

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Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 30, 1954.

third of the lobe symptoms of insufficiency do not usually appear. Indeed, as little as one-tenth of the anterior lobe may protect against the secondary insufficiency of the thyroid and adrenal glands. However, with greater destruction of the gland severe manifestations of insufficiency with nervous, mental, and metabolic changes appear.

CASE REPORT

A report of a patient illustrating the classic clinical picture of this syndrome associated with neurologic symptoms is presented.

A 32 year old white married housewife was admitted to the hospital on August 5, 1953 with the chief complaint of severe headache and episodes of unconsciousness.

Present illness: Following the birth of her second child 11 years previously this patient had a severe postpartum hemorrhage associated with fever and pelvic pain. She was unconscious for 11 hours at this time, and she received 1,500 cc. of blood. Lactation occurred at that time, but it was stopped therapeutically. Since this delivery the patient has had amenorrhea, complete loss of axillary and pubic hair, and loss of libido. She states that she had mild hot flashes at that time for a short period. She also noted dyspareunia and right lower quadrant pain. Headaches became more prominent, although they had preceded this illness.

For the past ten years she has noted increasing loss of energy, with somnolence, slight weight gain, dryness of the skin, and loss of the lateral portions of her eyebrows. During the past few years she has been sleeping approximately ten hours a day. Her weight increased by 20 pounds from 110 to 130.

Three years ago she first had an episode of unconsciousness which lasted for 30 minutes. This was not associated with convulsive movements. At this time it was observed that her pulse was 45 per minute, and she was given intravenous glucose. During the past two months two additional episodes of prolonged unconsciousness have occurred.

The onset of menses was at 13 years of age, with a regular 30 day cycle. The menstrual periods were of five days' duration and required two to three pads per day.

Physical examination: On admission she appeared drowsy, her face was puffy, and most of the hair of the eyebrows was absent. The skin was silky and dry and free of abnormal pigmentation. No axillary or pubic hair was present. The thyroid was not palpable. The pulse varied between 45 and 60 per minute. Blood pressure was 100/60. There was no cardiac enlargement. The breasts were of normal size. The skin of the vulva and vagina was thin with senile vaginitis. Culdoscopy revealed atrophy of the ovaries and uterus.

Neurologic examination revealed that the pupils were equal and reacted normally to light. The fundi were normal as were the visual fields. The reflexes showed a prolonged relaxation phase after contraction.

Laboratory studies gave the following information: Hemoglobin 11.7 gm. per cent; white blood count 7,100 cells per cu. mm. with a differential of 44 per cent polymorphonuclears, 2 per cent eosinophils, 42 per cent lymphocytes, and 12 per cent monocytes. Serologic test for syphilis was negative. Blood urea nitrogen was 13 mg. per cent. The total cholesterol was 270 mg. per cent, of which 32.6 per cent was free. Urinalysis was negative. Serum sodium was 140 mEq/1, potassium was 3.8 mEq./1, chloride was 102.6 mEq./1. Basal metabolic rate was minus 29 per cent. A glucose tolerance test revealed the following: Fasting: 57 mg. per cent; two hours, 65 mg. per cent; three hours, 53 mg. per cent; four hours, 60 mg. per cent; and five hours, 65 mg. per cent.

Water test revealed that the 12-hour urine total was 600 cc. at 5:00 a.m. After 1,140 cc. of water was given, the urine output at 6:00 a.m. was 15 cc.; at 7:00 a.m., 25 cc.; and at 8:00 a.m., 30 cc. The results of the salt deprivation test are shown in table 1. With fall of the serum sodium from 139 to 130.7 mEq/1, the test was stopped.

TABLE 1
SALT DEPRIVATION TEST

Date:	8/10	8/11	8/12	8/13	8/14
Serum sodium level mEq/1	139	137	135	135	130.7
Intake—mEq. Na	98	98	51	45	45
Output—mEq. Na	91	87	75	10.5	17.4

Roentgenograms of the skull were normal. The electroencephalogram was abnormal, with three to seven cycle per second waves in all leads. There was no focal abnormality.

The electrocardiogram showed a normal sinus rhythm of 45 per minute with a normal tracing. X-ray studies of the chest and abdomen and intravenous pyelograms were all normal. An endometrial biopsy revealed relatively atrophic endometrium showing slight evidence of proliferative activity.

This patient presented evidence of decreased ovarian, thyroid, and adrenal cortical function secondary to postpartum pituitary necrosis. She was placed on cortisone therapy, 25 mg. a day orally in two divided doses. After two days on cortisone the patient was started on thyroid, 30 mg. daily. After a few days on this combined therapy marked clinical improvement was noted. She became more alert. The facial edema disappeared and expression appeared brighter. Since then the thyroid medication has been increased to 100 mg. daily, and she has also been placed on testosterone, 10 mg. daily sublingually. Two months after discharge she obtained a position and was able to work full time for a period of approximately two months. She is able to do all of her housework. Her weight has remained relatively constant. There have been no episodes of unconsciousness during a nine month follow-up period.

DISCUSSION

Sheehan[7] has recently reported the results of oral cortisone therapy in four patients with postpartum pituitary insufficiency. They were treated with 12.5 mg. of cortisone daily for two years with no episodes of coma, convulsions, or other signs of progression. The average duration of life in 35 cases of puerperal necrosis was 14 years. Therefore, the ultimate value of replacement therapy is not yet known.

This clinical syndrome may present the symptoms of dullness, forgetfulness, lack of initiative, depression, and convulsions. Of the proved cases more than half had terminal attacks of coma. A number of the patients died in the first attack. Periods of weakness, restlessness, and delirium precede attacks of coma. There are two types of disturbance which lead to coma, hypoglycemia and hyponatremia. With hypoglycemia there may be deep coma with low body temperature, slow pulse, and low blood pressure. In such patients the administration of glucose intravenously produces rapid improvement. In episodes of coma related to adrenal cortical insufficiency there is a satisfactory response to hypertonic saline solution. It is important to separate hypoglycemia occurring in this clinical syndrome from that due to an islet cell tumor of the pancreas or to functional hypoglycemia.

SUMMARY

A case of postpartum pituitary insufficiency illustrates the chief clinical features, neurologic aspects, and available therapy for this disorder.

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CASE REPORT

Chronic Extradural Hematoma of the Posterior Fossa

A Case with a Diagnostic Pneumoencephalographic Finding

Neal Aronson, M.D. and Joseph Ransohoff, M.D.

EXTRADURAL HEMATOMA of the posterior fossa is always caused by trauma and almost invariably presents as an acute problem. There are many excellent reports on the acute form of this condition.[1–6, 8–14, 16–21, 24] Only one chronic case has appeared in the literature. This was reported by Turnbull in 1944.[22] The present case represents the second of this type. A previously unreported and probably diagnostic pneumoencephalographic finding was discovered in this case and will be mentioned.

PRESENTATION OF CASE

A 42 year old right-handed housewife was admitted to the Neurological Institute for the first time on December 1, 1953. Her chief complaints were left-sided and vertex headaches of six to seven weeks' duration, and visual difficulty of at least ten days' duration. She was partially disoriented, hallucinating actively, had little insight as to her condition, and was unreliable in anamnesis.

Present illness: About a year prior to hospital admission her husband first noted that her gait was becoming unsteady and that she tended to veer to the left. She also began to have difficulty in fine coordinated acts, such as applying a match to a cigarette. Five months later she began dropping things involuntarily and some slurring of speech supervened, and about a month after that she began to complain of pain in the suboccipital region. Six weeks before hospital admission these headaches became generalized and severe, and were accompanied for the first time by intermittent vomiting. There was a vague history of some sort of seizure about a week prior to admission, followed by a fall in which she struck her head, but no external evidence of trauma had resulted from this blow.

History: The patient smoked approximately ten cigarettes a day and had been a moderately heavy drinker for some time, occasionally imbibing as much as a pint of alcohol a day.

She had had syphilis in 1928, which was adequately treated. Several negative serologic examinations had been recorded since that time. A hysterectomy was performed in 1933 for fibroids. She had suffered severe head trauma in 1939 in an automobile accident during which she was rendered unconscious. Examination revealed several scalp lacerations and contusions of the right frontal region, but skull films were said to be negative. Fractures of the lumbar spine,

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right clavicle, scapula, and several ribs were also discovered. General diagnoses of cerebral concussion and shock were made. However, the patient eventually recovered completely from this episode with no immediate neurologic sequelae. She had had a cholecystectomy in 1948.

Physical examination: The patient was a well developed and well nourished woman who was confused and having visual hallucinations. She had been receiving fairly high doses of sedation following the seizure which had occurred several days before her admission. When these drugs were discontinued her mental status rapidly cleared. Temperature was 99.6° F., pulse 80, respirations 20, and blood pressure 164/90. General examination was unremarkable except for moderate dehydration and scattered wheezes over both lung fields.

Neurologic examination: The gait was unsteady with a tendency to sway from side to side. Tandem walking was difficult, and there was moderate truncal ataxia. Although muscle power and tone were normal, the patient tended to fall backward and to the right in the Romberg position. There was a slight terminal tremor on finger-to-nose test bilaterally. Heel-to-knee and heel-along-shin tests were performed fairly well. There was no drift of the outstretched upper extremities. Succession movements were well done. Reflexes were normal and sensation was intact in all modalities. Examination of cranial nerves revealed bilateral papilledema of three diopters without hemorrhages or exudate, slight left abducens weakness, slight scanning of speech, and fine, sustained nystagmus on vertical and left and right lateral gaze. Moderate nuchal rigidity was noted, and the posterior cervical muscles were somewhat tender.

Laboratory data: Blood count, erythrocyte sedimentation rate, blood sugar, Mazzini reaction, and urinalysis were all within normal limits. The electroencephalogram was normal, and skull roentgenograms were normal except for a suggestion of demineralization of the posterior clinoids. The pineal was calcified and in normal position. Chest films were unrevealing except for evidence of old healed rib fractures.

Course: There was no essential change in the patient's status while under observation, except for clearing of hallucinations when sedation was decreased.

Ventriculogram: On December 14 ventriculography with 60 cc. of oxygen showed clear ventricular fluid under greatly increased pressure (total protein 12 mg. per cent; seven white blood cells per cu. mm.; 857 crenated red blood cells per cu. mm.; serology negative). The films disclosed dilatation of the lateral and third ventricles without shift, but the fourth ventricle and cisterna magna were not visualized. In order to demonstrate these structures, 20 cc. of oxygen was introduced by lumbar puncture in 5 cc. amounts, replacing an equal quantity of spinal fluid. Roentgenograms then showed that the fourth ventricle was slightly deviated to the right and anteriorly, but was normal in size and shape. The diagnosis of a probable posterior fossa mass lesion was made.

When the films were studied after operation, a comma-shaped posterior indentation of the cisterna magna was noted. The radiologist pointed out that the shape of the filling defect was characteristic of hematomas in general, as Dyke[7] had reported with regard to subdural hematomas of the supratentorial space. It should be mentioned that such a defect could be produced by either an extradural or subdural hematoma, since the indentation is produced by an extraarachnoidal mass regardless of whether it is intradural or extradural. This is the first time, we believe, that such a finding has been noted in a posterior fossa lesion (figure 1).

Operation: A suboccipital craniectomy was performed with the patient in the prone position. On trephining the skull, dark fluid escaped from the burr holes. When the craniectomy was completed, a large extradural hematoma presented, consisting of about 45 cc. of old organized blood, which

FIG. 1. Arrows indicate the comma-shaped posterior indentation of the cisterna magna. The slightly anteriorly dislocated fourth ventricle can also be seen.

was under increased pressure and tended to extrude itself. It overlay both cerebellar hemispheres, being slightly thicker on the left. There was some evidence of lamination, and whereas the major portion of the clot was solid and dark in color, a considerable portion was liquid and of different color, suggesting that there had been more than one episode of bleeding. It is conceivable that the first episode of bleeding had occurred as a result of the head trauma in 1939. In any case, the patient had had symptoms of a posterior fossa lesion for at least a year prior to this admission, attesting to the chronicity of the greater portion of this clot. There was no evidence of an old fracture line and the origin of the bleeding could not be determined. The clot was completely removed by suction and irrigation, and the dura was not opened.

The patient made a complete and uneventful recovery and was discharged on December 31. At that time examination of the fundi revealed only slight residual gliosis about the margins of the disks, suggesting that the papilledema had been of fairly long duration. The only other abnormal finding at that time was minimal bilateral intention tremor of the hands.

SUMMARY

1. A case of chronic extradural hematoma of the posterior fossa is presented, and is the second chronic case to be noted in the literature.

2. A previously unreported pneumoencephalographic finding is described, consisting of a comma-shaped posterior indentation of the cisterna magna which is felt to be diagnostic of the presence of hematoma in this location.

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PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY

Seventh Annual Meeting

April 25 - 30, 1955

Shamrock Hotel — *Houston, Texas*

Review Courses in Basic and Clinical Neurology

April 25, 26, 27, 1955

Intensive review courses in basic and clinical neurology will be given preceding the annual meeting, sponsored and arranged by the American Academy of Neurology. Courses will be held as follows:

Neuropathology—April 25, 1955

Neuroroentgenology—April 25, 1955

Electroencephalography—April 26, 1955

Neurophysiology—April 26, 1955

The Collagen Diseases—April 27, 1955

Neuromuscular Disorders—April 27, 1955

Additional information regarding these review courses may be obtained from Mrs. J. C. McKinley, Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

WEDNESDAY, APRIL 27, 1955

Evening Session 8:30 p.m.

A SYMPOSIUM OF INQUIRY

What We Need to Know About Central Nervous System Vascular Disease:

Physiology—Seymour S. Kety, *Bethesda, Maryland*

Pathology—Miller Fisher, *Montreal, Canada*

Neurology—Clark Millikan, *Rochester, Minnesota*

Internal Medicine—Irvine H. Page, *Cleveland, Ohio*

Summary—Adolph L. Sahs, *Iowa City, Iowa*

This is a carefully organized two hour session on vascular disease and related factors, with emphasis on the areas in which significant data are lacking, yet are greatly needed for better understanding of the disease. This symposium, a departure from the usual, is a group effort to provoke and promote research.

THURSDAY, APRIL 28, 1955

Morning Session 9:00 a.m.

Chairman: Robert B. Aird, *San Francisco, California*

Secretary: Bill Garoutte, *San Francisco, California*

Role of Isotopes in Neurology

Bill Garoutte, *San Francisco, California*

Neurologic Aspects of Compressed Air Illness

H. W. Gillen, *New London, Connecticut*

Neurologic Manifestations of Nasopharyngeal Tumors

Herbert E. Rosenbaum and William B. Seaman, *St. Louis, Missouri*

Amyloid Polyneuropathy—The Clinical Entity

John F. Sullivan and Thomas E. Twitchell, *Boston, Massachusetts*

The Electroencephalogram in Neurologic Practice

James L. O'Leary, *St. Louis, Missouri*

Business Session 11:30 a.m.

Howard D. Fabing, presiding

THURSDAY, APRIL 28, 1955

Afternoon Session 2:00 p.m.

Chairman: Francis M. Forster, *Washington, D.C.*

Secretary: Romeo R. Apostol, *Washington, D.C.*

PRESIDENTIAL ADDRESS

The Dimensions of Neurology

Howard D. Fabing

Cincinnati, Ohio

Observations on the Effect of Thorazine on Cells in Vitro

C. M. Pomerat, *Galveston, Texas*

Vomiting: Neural Mechanisms and Control by Chlorpromazine

William Amols and H. Houston Merritt, *New York City*

Effect of Thorazine Chlorpromazine on Human Spasticity and the Electromyogram

J. V. Basmajian and A. Szatmari, *Toronto, Canada*

Suppression of Auditory Nerve Activity during Stimulation of Efferent Fibers to the Cochlea

Robert Galambos, *Washington, D.C.*

Spike-and-Wave Discharges Produced by Electrical Stimulation of the Human Epileptic Cortex and Subcortex

Reginald G. Bickford, Patrick F. Donovan, Collin S. MacCarty and Haddow M. Keith, *Rochester, Minnesota*

Cerebral Effects of Psychosurgery

Marcus P. Rosenblum, Leroy Barnes and William Ehrlich, *Lyons, New Jersey*

FRIDAY, APRIL 29, 1955

Morning Session 9:00 a.m.

Chairman: Thomas W. Farmer, *Chapel Hill, North Carolina.*

Secretary: C. Capers Smith, *Chapel Hill, North Carolina*

Neurologic Complications of Pregnancy

Preston Robb, *Montreal, Canada*

Syndrome of Intermittent Basilar Artery Insufficiency

Robert G. Siekert and Clark H. Millikan, *Rochester, Minnesota*

Vascular Phenomena Involving Brainstem Structures—A Clinicopathologic Study

Harry C. H. Fang and J. J. Palmer, *Los Angeles, California*

Dental Hypoplasia in Cerebral Palsy—With Special Reference to the Incidence in Kernicterus

M. A. Perlstein, *Chicago, Illinois*

Myofacial Pain Syndromes

Andres E. Sola and Robert L. Williams, *San Antonio, Texas*

Nature and Significance of Pentosuria in Neurovascular Diseases

Donald B. Tower, Milton A. Pogorelskin and Edmund P. Peters, *Bethesda, Maryland*

JUNIOR PRIZE ESSAY

This is the annual prize awarded by the Women's Auxiliary of the American Academy of Neurology to the junior member who submitted the manuscript adjudged best by the prize committee.

Business Session 11:30 a.m.

Walter O. Klingman, presiding

FRIDAY, APRIL 29, 1955

Afternoon Session 2:00 p.m.

Chairman: A. L. Sahs, *Iowa City, Iowa*

Secretary: R. A. Utterback, *Iowa City, Iowa*

REPORTS OF UNUSUAL CLINICAL ENTITIES

Cerebral Schistosomiasis: Clinical Pathologic Correlations of 22 Cases and Follow-up Data

Richard G. Berry, *Philadelphia, Pennsylvania* and Lorenz E. Zimmerman, *Washington, D.C.*

Dystonia Associated with Generalized Muscular Atrophy: A Syndrome Noted in Two Patients

I. S. Freiman and Joachim Luwisch, *New York City*

Neurologic Symptoms with Osteoid Osteoma

Joseph G. Rushton and Donald W. Mulder, *Rochester, Minnesota*

Spontaneous Bilateral Labyrinthine Deficit

Joe R. Brown and J. B. McBean, *Rochester, Minnesota*

Mobius's Syndrome—Congenital Oculofacial Paralysis

Bertram E. Sprofkin and J. William Hillman, *Nashville, Tennessee*

Protrusion of Thoracic Intervertebral Disks

Kenneth H. Abbott, *Columbus, Ohio*

Spielmeyer-Vogt Disease

W. A. Butcher and Julius Hoffman, *Columbus, Ohio*

Clinical and Pathologic Study of a Family with Hereditary Cerebellar Ataxia

J. H. Chandler and José Bebin, *Ann Arbor, Michigan*

Light Induced Clinical and Electroencephalographic Abnormalities as Manifestations of Genetically Determined Cerebral Disease

Sherwood Davidson and C. Wesley Watson, *Boston, Massachusetts*

SATURDAY, APRIL 30, 1955

Morning Session 9:00 a.m.

Chairman: Fred L. Stone, *Pittsburgh, Pennsylvania*

Secretary: Junior Prize Essayist

Neurologic Manifestations of the Collagen Diseases—Diagnosis and Treatment

Gilbert H. Glaser, *New Haven, Connecticut*

Dermatomyositis Following Injection of Penicillin

Carl E. Arbesman, Irving Hyman and Kornel Terplan, *Buffalo, New York*

Neurologic Manifestations of Magnesium Depletion State

Walter O. Klingman and Cary Suter, *Charlottesville, Virginia*

Treatment of Headache with Reserpine

Arnold P. Friedman, *New York City*

Reserpine (Serpasil) Effects upon Epileptic Monkeys

Joseph G. Chusid, Lenore M. Kopeloff and Nicholas Kopeloff, *New York City*

Treatment of Bell's Palsy with Cortisone and Other Measures

Madison H. Thomas and Chester B. Powell, *Salt Lake City, Utah*

Peripheral Neuropathy Caused by Arsenical Intoxication—with Observations on the Therapeutic Effects of BAL

Albert Heyman, John B. Pfeiffer, Jr. and Robert W. Willett, *Durham, North Carolina*

Neurology

BOOK REVIEWS

Psychomotor Aspects of Mental Disease

H. E. King, Ph.D. 1954. Cambridge, Mass.: Harvard University Press. 156 pages. $3.50.

IN THIS MONOGRAPH the author, who is associate professor of psychiatry specializing in research psychology at Tulane University School of Medicine, has concerned himself with three basic characteristics of psychomotor (extrinsic motor) activity, namely 1) reaction time, or speed of initiating movement, 2) speed of tapping, and 3) finger dexterity. He has also studied "disjunctive reaction time" in more complicated tapping tests, and speed of motor response in discrimination between bell and buzzer. Normal persons of both sexes at varying ages exhibited levels of performance and learning curves in agreement with results reported by others. He next applied the tests to three groups of psychiatric patients - schizophrenics, " pseudoneurotic" schizophrenics, and neurotic persons - and correlated the degree of clinical psychiatric abnormality with the test performance.

The learning curves in all three groups were closely similar to the normal, but in all tests the schizophrenics revealed distinct retardation, the pseudoneurotic schizophrenics a less marked retardation, and the neurotic patients essentially normal speeds. Further, there was a positive correlation between the severity of psychiatric abnormality and the degree of motor retardation.

The author believes, on the basis of his own studies and those of others, that the motor retardation exhibited by the patients is probably not secondary to mental disorganization (withdrawal, preoccupation, etc.), but is rather indicative of a primary disturbance in a basic adaptational process of adjustment. Although admittting that further proof is needed, he concludes that "psychomotility is . . . a fundamental psychologic component and primary adaptive characteristic of life," and that "retarded and faulty psychomotor response is . . . a basic indication of . . . psychobiologic maladaption."

The clinician's reaction to this research is complex. He is not surprised at the results; he marvels at the patience and endurance which have been so lavishly expended for findings that might have been anticipated. There can be no cavil about the accuracy and reliability of the work, but its interpretation is difficult. In the first place, reduced reaction time, speed of movement, and dexterity are common in many nonpsychiatric conditions, and may arise from diverse causes, such as myxedema, intoxications, or palsies. Further, every neurologist knows that practice makes perfect, so that typists, pianists, jewellers, all who work delicately with their fingers, are speedier and more dexterous than are heavy laborers, aside from any reference to psychiatric status. In the second place, though it is evident from this work that schizophrenics are slow in movement, it is

not at all clear what this has to do with schizophrenia, in which the essential flaw seems to be a qualitative error in evaluation rather than a quantitative defect such as retardation. Hence the clinician is apt to doubt that the retardation so thoroughly documented here is part of the basic disorder of schizophrenia, or contributes in any way to its unique behavioral features.

But the truth is to be respected. This book fully records the results of meticulous work, and therefore adds something to our fund of knowledge. When interpreted, that something may yet prove to be important.

R. P. M.

Textbook of Pediatrics

Waldo E. Nelson, M.D., Editor. 1954. Philadelphia: W. B. Saunders Company. 1,581 pages. $15.00.

IT IS OBVIOUS at the outset that the editor of this volume was intent on making the text as representative of current pediatric thought and practice as possible. A large number of contributors, with extensive personal experience and knowledge of various facets of pediatric medicine, give the book an unmistakable air of authority.

This is a very comprehensive book, as one would expect in a complete treatise on a subject as broad as pediatrics. Naturally there are many subjects which blend with other specialty fields. For instance, there is a section on the nervous system which occupies 75 pages and covers nervous disorders from infancy through adolescence in considerable detail. There is, in addition, an excellent section on convulsive disorders. The book is so extensive in subject matter that it will serve as an excellent source of information not only for general practitioners and pediatricians, but for others in various specialties who deal with children in their practice.

The text is well printed and liberally illustrated. Each section has an extensive bibliography and there is an adequate subject index. All-in-all, this volume maintains the high quality set by previous editions.

R. H. E.

Die zerebrale Angiographie

H. Krayenbühl and H. R. Richter. 1952. Stuttgart: Georg Thieme Verlag, 217 pages, 100 illustrations.

SINCE THE invention of carotid arteriography by Moniz in 1927, increasingly more cerebral arterial and venous angiograms have been made in neurologic clinics all over the world, while the frequency of pneumographic studies of the brain has declined correspondingly. Each type of neuroradiologic examination has its definite role, and angiography supplements but does not supplant other diagnostic technics.

European neurologists and neurosurgeons preceded their American confreres in widespread adoption of cerebral angiography in clinical practice. Professor Hugo Krayenbühl was able to select illustrations for *Die zerebrale Angiographie* from more than 1,500 angiographic examinations done on his neurosurgical service at Zürich.

Technics, characteristic vascular patterns, and other details of intracranial angiography are discussed in practical fashion but it is in the clearcut photographic presentation of actual angiograms, normal and pathologic, that the greatest value of this volume lies. Accompanying artist's sketches point up significant roentgenographic findings.

Die zerebrale Angiographie is an interesting and informative monograph which should be in the possession of every neurologist and neurosurgeon and will be a handbook of ready and valuable reference in radiologic libraries. The illustrations, format, and print are attractive and readable. The text is in German.

J. P. M.

NEWSLETTER

MARCH, 1955

Howard D. Fabing, President
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AMERICAN ACADEMY OF NEUROLOGY

Irvine Page to Join AAN Symposium Dr. Irvine H. Page, president-elect of the American Heart Association, will participate in the symposium on "What We Need to Know About Central Nervous System Vascular Disease" to be held at the 1955 annual meeting of the Academy in the Shamrock Hotel, Houston, April 27. Though not previously publicized, this symposium of inquiry has been carefully planned for months by Augustus S. Rose and his colleagues of the AAN research committee. Its primary purpose is to provoke and promote more research in this relatively neglected field. Madison H. Thomas and Joe R. Brown of the research committee are preparing special questions for key interrogators in the audience to uncover the important unknowns in central nervous systems vascular disease. With Dr. Rose acting as chairman, the slate of speakers includes Seymour S. Kety (physiology); Miller Fisher (pathology); Clark Millikan (neurology); and Irvine H. Page (internal medicine). The presentation by Dr. Page is especially anticipated because of his vast experience in cardiovascular and chemical research, which includes work as director of chemical research at the Kaiser Wilhelm Institute, an associate member of the Rockefeller Institute, director of the Lilly Laboratory of Clinical Research at Indianapolis City Hospital, and since 1945 director of research at the Cleveland clinic.... Following the final presentation, a summary of the symposium will be given by Adolph L. Sahs. Arrangements for tape recording and a transcription of the proceedings are being made by Jerome K. Merlis.

DeJong Returns From England Russell N. DeJong, editor of Neurology, recently returned from a six month visit to neurologic centers in Great Britain and Europe under a Fulbright Scholarship. Primary purpose of his visit was to study teaching methods abroad, particularly at the Institute of Neurology, the National Hospital, Queen Square, London. Here he studied methods and participated in ward rounds and conferences with members of the Queen Square staff, including Sir Francis M. R. Walshe. Sir Charles Symonds, and Doctors Macdonald Critchley, J. Purdon Martin, and E. A. Carmichael. Dr. DeJong was particularly attracted to the activities of the neurologic research unit under the direction of Dr. Carmichael and spon-

sored by the British Medical Research Council. Some of the active projects in this unit are: studies on hemispherectomies, (Bates, Cobb, Zangwell, and others); neuro-otologic studies, (Hallpike and Dix); clinical neuroanatomic studies, (Smith and Nathan); electrical reactions in nerve transmission, (Dawson and Gilliat); and electromyographic studies, (Ian Simpson). Still another item of particular interest to Dr. DeJong was the detailed and extensive clinical studies on parietal lobe lesions conducted by Dr. Macdonald Critchley. While in London he also had the opportunity to attend various medical meetings, including that of the Royal College of Physicians (Sir Russell Brain is currently president), and was a guest at the Harverian Oration, delivered by Sir Charles Symonds.... Other neurologic centers in England visited by Dr. DeJong were the neurologic service at the London Hospital, (Sir Russell Brain and Dr. R. A. Henson); the neuropathologic unit of Dr. Dorothy S. Russell; the Maudsley Hospital, where extensive work on epilepsy and temporal lobe lesions is being conducted by Mr. Murray Falconer and Doctors Denis Hill and Desmond Pond; the National Spinal Injuries Center at the Stoke-Mandeville Hospital (under the direction of Dr. Ludwig Guttmann); and the neurologic service of Dr. W. Ritchie Russell at the University of Oxford.... Dr. DeJong also had occasion to visit and lecture at the medical schools of the Universities of Aberdeen and Edinburgh in Scotland and the Universities of Groningen, Utrecht, Amsterdam, and Leiden, the latter tour having been arranged through the courtesy of the student medical association.

Mr. Cohen Presents Check To Academy President Howard D. Fabing announces that on December 14, Mr. L. M. Cohen, publisher of NEUROLOGY, presented him a check made out to the American Academy of Neurology, representing 50% of the profit which the journal made during the previous year. In commenting on the donation, President Fabing said, "I know that members of the Academy appreciate this contribution. We are very lucky people to have such a fine friend as our publisher."

* * * * * *

New Diplomates In Neurology At the annual examination of the American Board of Psychiatry and Neurology held in New York City (Dec. 13-14), 11 candidates were certified in neurology. The successful candidates are: Maynard M. Cohen, Minneapolis; Thomas Claiborne Guthrie, New York City; James Francis Hammill, Silver Spring, Md.; Simon Horenstein, Boston; Robert Jaffe, New York City; Peritz Scheinberg, Miami; Robert George Siekert, Rochester, Minn.; Jolyon Simeon Tucker, Birmingham, Ala.; Philip Taylor White, Indianapolis. Certified in psychiatry and neurology are Edward Peirson Richardson, Jr.,

Boston, and Herbert Weiner, Silver Spring, Md..... The next Board examination will be held in New Orleans, February 28 - March 1.

Neuropathologists to Meet in London The Second International Congress of Neuropathology, now being organized by the British committee to the congress, will be held in London (Sept. 12-17). Preliminary plans call for both plenary and free sessions at the congress. At the preliminary meeting of the executive program committee in London (July 15, 1954), the subjects proposed for the plenary sessions were: cytochemistry of the neuron in relation to injury and other environmental changes, excluding lipoidoses; the blood-brain barrier in inflamation and allergy; problems in the malignancy of gliomas. For the free sessions, presentations not exceeding 10 to 15 minutes in length may be submitted by members of the American Association of Neuropathologists, the American Neurological Association, American Psychiatric Association, and the American Association of Pathologists, to the chairman of the American Committee, Dr. Armando Ferraro, 722 West 168th Street, New York 32.... Messrs. Thos. Cook & Son, Ltd., have been appointed as official travel agents for the Congress.

Neurosurgeons to Convene in Montevideo The Sixth Latin-American Neurosurgical Congress, under the patronage of the Republic of Uruguay, will be held in Montevideo, March 21-24. The program will highlight reports on cisternal herniations, pain surgery, dyskinesias, and a symposium on the thalamus. Official participants from the U.S.A. and Canada include Percival Bailey, Herbert Jasper, H. W. Magoun, and A. Earl Walker. The Secretary General of the congress is Dr. R. Arana-Iniguez, Convencion, 1287, Montevideo, Uruguay.... The South American Electroencephalography Congress will also meet in Montevideo at the same time.

Sweeney New President of Neurosurgical Congress At the fourth annual meeting of the Congress of Neurological Surgeons, held at the Waldorf-Astoria Hotel, New York City (November 4-6, 1954), Dr. Donald B. Sweeney (Birmingham, Ala.) was elected president; Dr. Bland W. Cannon (Memphis), vice president; and Dr. Philip D. Gordy (Wilmington, Del.), secretary-treasurer. Members of the executive committee are Doctors M. P. Sayers (Columbus) and Robert Mabon (Atlanta).

Neurologic Institute to be Established in Caracas Plans are under way for the establishment of a national neurologic institute in Caracas, Venezuela, under the direction of Dr. Humberto Fernandez Moran, formerly associated with

the Karolinska Institute in Sweden. The new institute is designed to provide patients with complete neurologic and neurosurgical treatment, as well as training and research facilities in these fields. The research activities comprise fundamental research and applied clinical research. Structurally the new institute is based on the plans of the neurologic and neurosurgical clinics which will be annexed to the Karolinska Hospital in Stockholm and were designed by the Swedish architect, Hakon Ahlberg, who recently visited neurologic centers in the U.S.A.

Briefs The 1955 annual meeting of the Harvey Cushing Society will take place at the Chateau Frontenac, Quebec, (May 16-18).... Drs. Albert Szent-Gyorgyi, Otto Loewi, and Harriett Edgeworth have been elected as honorary members to the medical advisory board of the Myasthenia Gravis Foundation.... Plastic disk recordings on the origin and control of epilepsy, featuring presentations by William G. Lennox, are now available at the Medical Dental Educational Recording Corporation, 421 W. School Lane, Philadelphia 44, Pa..... A. B. Baker has been awarded a grant of $5,250 for continued muscular dystrophy research by the Minnesota Ladies Auxiliary of the Grand Aerie Fraternal Order of Eagles. This grant program in the division of neurology of the University of Minnesota is under the immediate supervision of Dr. Ian Brown. Dr. Brown is making a study, under the auspices of the Muscular Dystrophy Associations of America, to confirm or disprove previous investigators' preliminary observations on the efficacy of various protein and vitamin regimens as therapy for muscular dystrophy.....

Percy Bailey

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NEUROROENTGENOLOGY—April 25, 1955. Dr. A. L. Sahs, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $20.00; Non-members: $25.00.

ELECTROENCEPHALOGRAPHY—April 26, 1955. Dr. V. R. Zarling, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPHYSIOLOGY—April 26, 1955. Dr. James L. O'Leary, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

THE COLLAGEN DISEASES—April 27, 1955. Dr. Joe R. Brown, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROMUSCULAR DISORDERS—April 27, 1955. Dr. G. Milton Shy, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

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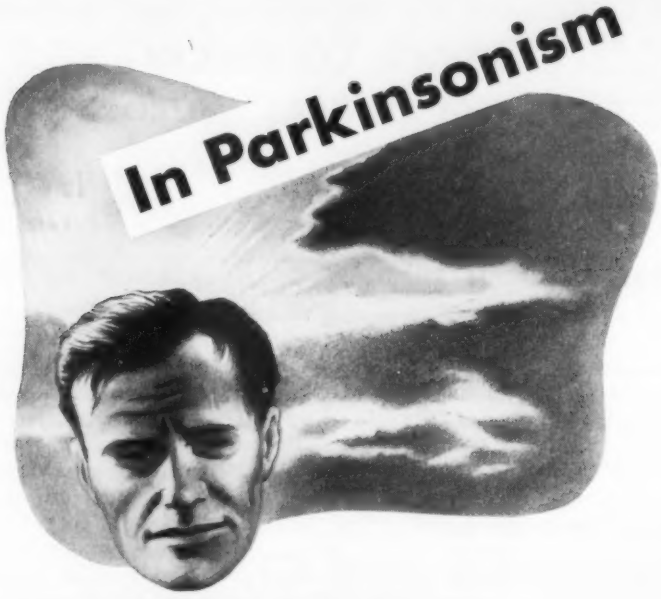

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1. Am. J. Pharm. — 117:319-326, 1945 2. N. Y. State Journal of Medicine 49/1285
3. Conference National Academy of Sciences Sept. 9, 1950

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BROAD SPECTRUM ANTIBIOTICS

The new broad range antibiotics differ in their activity against specific diseases more widely than has been generally recognized, Henry Welch, Director of Antibiotics of the Food and Drug Administration, told a group of visiting foreign health officers recently at an antibiotics symposium sponsored by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

"Because of the close similarity of the chemical structure of the tetracyclines there has been a tendency to substitute clinically one for the other on the basis that these drugs have equal antibacterial activity," he warned. He presented laboratory data from Food and Drug Administration laboratories showing how widely Aureomycin (chlortetracycline), Terramycin (oxytetracycline) and tetracycline, the new antibiotic produced by removing a chlorine atom from the molecule of Aureomycin, differ in their effectiveness against various disease germs.

The huge antibiotic industry is only ten years old, Dr. Welch pointed out, recalling that in 1941 there was insufficient penicillin in the United States to treat a single case. Dr. Welch traced the phenomenal rise of antibiotics since World War II. Of 3500 different antibiotic substances isolated and studied since 1942, the great majority have not been found useful because of low potency or high toxicity, but about 15 have proved medically useful.

It has been estimated that in dollars spent for prescription drugs in recent years, conservatively 40 per cent of all prescriptions written include one or more antibiotics. Dr. Welch listed 43 infectious diseases and classes of diseases now controlled by antibiotics, and cited figures to show how they have cut the death toll from many formerly dreaded diseases.

COMPOCILLIN ORAL SUSPENSION

A ready-mixed oral suspension of the penicillin salt of hydrabamine has been introduced by Abbott Laboratories, North Chicago. This new preparation, marketed under the trade name, Compocillin, remains stable at least 12 months and has an appealing fresh banana smell and taste.

(Continued on page 18A)

McFarland Hall is the open unit of this private psychiatric hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

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S & D RELEASE GAMMA GLOBULIN

Poliomyelitis immune globulin (human), the new name asigned to gamma globulin by the National Institutes of Health, has been released to usual medical and drug channels by Sharp & Dohme, West Point, Pennsylvania, Division of Merck & Co., Inc. The product is available in 2 cc. and 10 cc. vials.

Each lot of poliomyelitis immune globulin represents a pooling of material from at least 2,000 donors. It is treated with ultraviolet radiation and processed to contain 16.5 gm. of globulin per 100 cc. The average blood donation yields approximately a single recommended dose for the prophylaxis of poliomyelitis in a six to seven year old child. Poliomyelitis immune globulin (human) confers temporary protection against the paralytic form of poliomyelitis or modifies the severity of paralysis. In other words, it is used as a prophylactic measure when an individual has been exposed, or when the incidence of poliomyelitis is high and there is the possibility of being exposed.

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*Textbook of Pharmacology, (Saunders) 1952.

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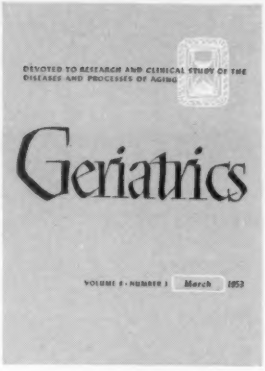

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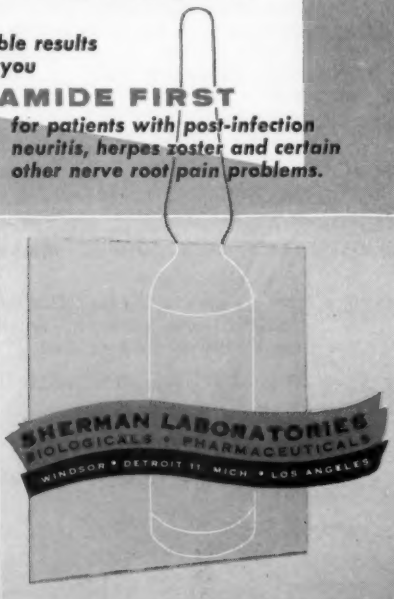
*Smith, R. T., New York Med. 8:16, 1952.



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Kinross-Wright, V.: Postgrad. Med. 16:297 (Oct.) 1954.

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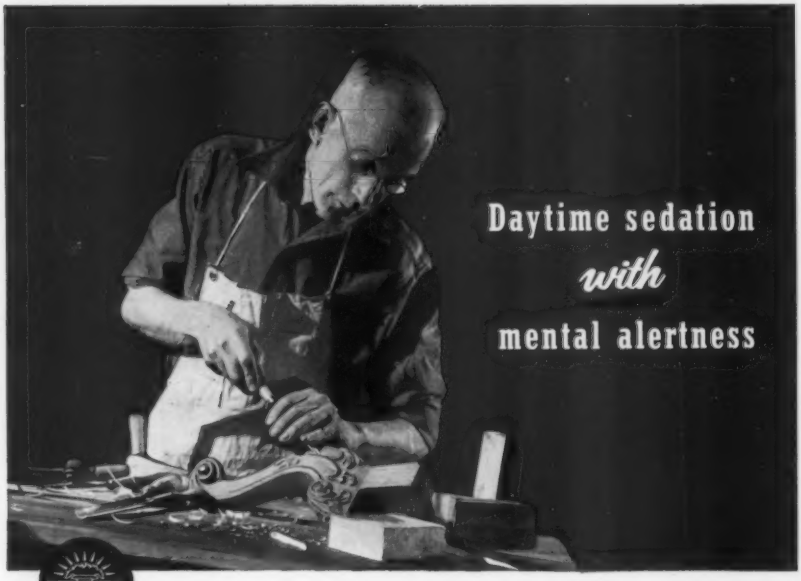
Smith, Kline & French Laboratories

1530 Spring Garden St., Philadelphia 1

**Trademark for S.K.F.'s brand of chlorpromazine hydrochloride. Chemically it is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride.*



MEBARAL®

BRAND OF MEPHOBARBITAL

—in depressed and agitated states

psychoneurosis
hypertension
hyperthyroidism
convulsive disorders
difficult menopause
hyperhidrosis

Neurotic depression hiding beneath the disguise of multiple physical complaints is an everyday problem in medical practice.

For effective sedation in these cases, and as a means of restoring harmonious relations between patient and environment, Mebaral has been found especially suitable because it lacks excessive hypnotic action.

DOSAGE:

Adults—32 mg. to 0.1 Gm. (optimal 50 mg.), 3 or 4 times daily.

Children—16 to 32 mg., 3 or 4 times daily.

SUPPLIED:

Tablets of 32 mg. (½ grain)
50 mg. (¾ grain)
0.1 Gm. (1½ grains)
0.2 Gm. (3 grains) scored

Mebaral, trademark reg. U. S. & Canada

WINTHROP-STEARNS INC.